DRUGS OF CHOICE 1960-1961

Walter Modell, M.D., Editor

Director, Clinical Pharmacology, and Associate Professor of Pharmacology, Cornell University Medical College, Attending Physician, New York Veterans Administration Hospital, Associate Visiting Physician Bellevue Hospital Member, Poison Control Advisory Board of New York City, Member, Revision Committee, United States Pharmacopeia XVI, Editor, Clinical Pharmacology and Therapeutics

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CONTRIBUTORS

THOMAS P ALMY M D

Professor of Medicine Cornell University Medical College Director of Second (Cornell) Medical Division Bellevue Hospital New York N Y

JOSEPH F ARTUSIO Jr M D

Professor of Anesthesiology in Surgery and Professor of Anesthesiology in Obstetr and Gynecology Cornell University Medical College Anesthesiologist in Chief New York Hospital New York N Y

ALVAN L. BARACH M D

Clinical Professor of Medicine College of Physicians and Surgeons Columbia University Associate Attending Physician Presbyterian Hospital New York N Y

DAVID PRESWICK BARR M D LL D Sc D

Professor (Emeritus) of Medicine Cornell University Medical College Consulting Physician to the New York Hospital New York N Y

WILLIAM B BEAN M D

Professor and Head of the Department of Internal Medicine College of Medicine State University of Iowa Physician in Chief University Hospitals Iowa City Senior Medico Consultant Veterans Administration Hospitals Iowa City and Des Moines Iowa

HYLAN A BICKERMAN M D

Associate Clinical Professor of Medicine College of Physicians and Surgeons Columbia University Visiting Physician Columbia University Research Division Goldwater Memorial Hospital New York N Y

JOHN J BONICA M D

Director of the Department of Anesthesiology and Pain Clinic Tacoma General Hospital and Pierce County Hospital Clinical Associate in Anatomy and Consultant to the Department of Anesthesiology University of Washington School of Medicine Senior Consultant in Anesthesiology Madigan Army Hospital and American Lake Veterans Administration Hospital Tacoma Wash

KEEN CATTELL Ph D M D

Professor (Emeritus) of Pharmacology Cornell University Medical College New York N Y

CHOWDHURY M B D Phil

School of Tropical Medicine Calcutta India

LEIGHTON E CLUFF M D

Associate Professor of Medicine and Head Division of Infectious Disease and Allergy Department of Medicine The Johns Hopkins University School of Medicine Physician The Johns Hopkins Hospital Baltimore Md

WILLIAM DAMESHEK, M D

Professor of Medicine Tufts University School of Medicine Senior Physician and Chief of Hematology New England Center Hospital Editor in Chief Blood The Journal of Hematology Boston Mass

M EDWARD DAVIS M D

Joseph Bolivar DeLee Professor and Chairman of the Department of Obstetrics and Gynecology University of Chicago Chief Chicago Lying in Hospital Chicago Ill

ALAN K DONE M D

Assistant Professor of Pediatrics Stanford University School of Medicine Stanford Calif

FREDERICK R FRANKE M D D Sc (Med)

Assistant Professor of Medicine School of Medicine University of Pittsburgh Pittsburgh Pa

DALE G FRIEND M D

Assistant Professor of Medicine Harvard Medical School Clinical Pharmacologist Peter Bent Brigham Hospital Boston Mass

NICHOLAS W FUGO Ph D, M D

Associate Professor of Obstetrics and Gynecology University of Chicago and Chicago Lying in Hospital Chicago Ill

JAMES T HAMLIN III, M D

Research Fellow in Medicine Harvard Medical School and Assistant in Medicine, Peter Bent Brigham Hospital Boston Mass

ROBERT G HEATH M D

Professor and Chairman of the Department of Psychiatry and Neurology Tulane University School of Medicine Senior Visiting Physician Charity Hospital of Louisiana New Orleans La

CHARLES H HEIDER M D

Department of Internal Medicine Hahnemann Medical College and Hospital of Philadelphia Philadelphia Pa

PAUL H HOCH M D

Commissioner of Mental Hygiene State of New York Professor of Clinical Psychiatry College of Physicians and Surgeons Columbia University New York N Y

ALBERT H HOLLAND Jr M D

Formerly Medical Director Food and Drug Administration Washington D C

SIBLEY W HOOBLER M D

Professor of Internal Medicine University of Michigan Medical School Director of the Hypertension Unit University of Michigan Hospital Ann Arbor Mich

CONTRIBUTORS

DAVID A KARNOFSKY, M D

Member Sloan Kettering Institute Associate Professor of Medicine Cornell University Medical College Attending Physician Chemotherapy Service D Medicine Memorial and James Ewing Hospitals New York N Y

B H KEAN M D

Associate Professor of Clinical Medicine (Tropical Medicine) Cornell Univers Medical College New York N Y

CHESTER S KEEFER M D

Professor of Medicine Boston University School of Medicine Physician in Chief Massachusetts Memorial Hospitals Boston Mass

HERBERT S KUPPERMAN Ph.D M D

Associate Professor of Medicine New York University Bellevue Medical Center New York N Y

LOUIS LASAGNA M D

Associate Professor of Medicine and Associate Professor of Pharmacology and Experimental Therapeutics Johns Hopkins University School of Medicine Baltimore Md

DONALD D LATHROP M D

Assistant in Psychiatry Department of Psychiatry and Neurology Louisiana State University School of Medicine New Orleans La

IRVING H LEOPOLD M D

Professor and Chairman Department of Ophthalmology The Graduate School of Medicine University of Pennsylvania Director of Research and Attending Surgeon Wills Eye Hospital Philadelphia Pa

ROBERT LICH Jr M D M S (Path)

Professor and Chairman of the Section on Urology Department of Surgery University of Louisville School of Medicine Louisville Ky

T A LOOMIS Ph D M D

Professor of Pharmacology School of Medicine University of Washington Seattle Wash

WILLIAM McFARLAND M D Commander U S Navy

Head Department of Clinical Hematology National Naval Medical Center Bethesda Md

PAUL L McLAIN M D

Professor of Physiology and Pharmacology School of Medicine University of Pittsburgh Pittsburgh Pa

LOYD C MILLER Ph D

Director of Revision Pharmacopeia of the United States New York N Y

WIS C. MILLS M D

Associate Professor of Medicine Hahnemann Medical College and Hospital of Philadelphia Philadelphia Pa

WALTER MODELL, M D

Associate Professor of Pharmacology, Cornell University Medical College, Attending Physician New York Veterans Administration Hospital, Associate Visiting Physician, Bellevue Hospital, Member, Poison Control Advisory Board of New York City, Member, Revision Committee, United States Pharmacopeia XVI, Editor, Clinical Pharmacology and Therapeutics, New York, N Y

JOHN H. MOYER M D

Professor of Medicine and Chairman of the Department of Internal Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa

PHILIP B PRICE, M D

Dean University of Utah College of Medicine, Salt Lake City, Utah

TRACY JACKSON PUTNAM, M D

Formerly Professor of Neurology, Harvard Medical School, Chief of the Department of Neurosurgery, Cedars of Lebanon Hospital, Los Angeles, Calif

GEORGE G READER, M D

Professor of Medicine, Cornell University Medical College, New York, N Y

WILLIAM H SAUNDERS, M D

Associate Professor of Otolaryngology, University Hospital, Ohio State University, Columbus Ohio

EDWARD B SCHLESINGER, M D

Attending Neurological Surgeon, Columbia Presbyterian Medical Center, Assistant Professor of Clinical Neurological Surgery, College of Physicians and Surgeons, Columbia University New York, N Y

PAUL K SMITH Ph D

Professor of Pharmacology and Executive Officer, School of Medicine, The George Washington University Consultant in Therapeutics, District of Columbia General Hospital and The George Washington University Hospital Member, Tri-Service Motion Sickness Committee, Washington, D C

HERMAN STEINBERG, M D.

Instructor in Medicine, Cornell University Medical College, New York, N Y

MARION B SULZBERGER, M D

[illegible] New York
[illegible] tologic Service,
[illegible] enter, New York, N Y

JOHN H TALBOTT, M D

[illegible]

WILLIAM L WILSON, M D

Assistant Professor of Medicine Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa

HOW I CAN MAKE A PATIENT VOMIT, and how I can purge or sweat him, are matters which a druggist's shopboy can tell me offhand When, however, I must use one sort of medicine in preference to another, requires an informant of a different kind—a man *who has no little practice in the arena of* his profession

—SYDENHAM *(1624-1689)*

PREFACE TO 1960-1961 EDITION

The warm reception given *Drugs of Choice, 1958-1959* proved that members of the medical profession recognize the present urgent need for authoritative and unbiased information on the choice of a particular drug for a particular clinical situation. This was gratifying to the thirty-seven contributors who gave their time to make an up-to-date book of this type possible. A well-timed revision is, however, essential if the book is to remain useful by being sufficiently up to date.

After thoughtful consideration, a two-year interval was selected for the revision period. A shorter period would be too brief for substantial experience with the drugs introduced in the interval and there would be too few new drugs to merit a new edition, whereas a longer period would allow the current edition to become badly dated long before a new one was available.

In the present book there are eight new chapters. The Physical and Chemical Considerations in the Choice of Drugs, The Choice of a Local Antiseptic, The Choice of Drugs for Viral, Spirochetal, and Rickettsial Infections, The Choice of Sedatives and Tranquilizers in General Medical Practice, The Choice of an Anorexiant, The Choice of Drugs in Endocrine Dysfunction, The Choice of Drugs for Ophthalmic Use, and The Choice of Drugs for Otolaryngologic Disorders.

In order to provide fresh insights and a forum for different points of view, it was originally planned to change the authorship of a few chapters, especially those on controversial issues, in each edition; consequently, three chapters in this edition are written by new authors. Thirteen new names will be found in the list of eminent contributors, the total now stands at forty-seven.

In this edition, a single alphabetically arranged all-inclusive Drug Index is used in preference to the separate specialized lists of drugs which followed the individual chapters in the original book. Drugs not mentioned or evaluated in the text are likely to be found in the Drug Index, but they will not appear in the general subject index, which includes page references for only those drugs described in the text.

Failure to discuss a new drug in the text may be interpreted to mean that the drug was introduced too recently to provide experience for a substantial opinion. Failure to discuss an older drug may be interpreted to mean that it is not a drug of choice and, in the author's opinion, is not of sufficient importance to merit discussion.

New York

WALTER MODELL, M.D.

PREFACE TO 1958-1959 EDITION

This book is a practical guide to the selection of the best drug for a particular therapeutic problem Due to the extremely fertile mating of the synthetic chemist and the pharmaceutical manufacturer, drugs appear on the market almost too quickly to learn the names to say nothing of distinguishing which are the same drugs with different proprietary names It is a Herculean job to learn enough about them to evaluate their relative therapeutic merits Yet the choice of a drug will determine whether the patient will receive the most judicious therapy

There are real advantages in choosing the best drug for the clinical problem at the outset of treatment For the seriously ill patient, time may be precious, and, if the first choice is the best drug for the situation, that irretrievable commodity is not wasted Something short of the best may provide incomplete relief, no relief at all, untoward effects, or disaster The patient is likely to assume, and perhaps he also has the right to expect, that his physician will provide the optimum drug for his condition the first time he writes a prescription It is understandable that, having endured a period of unsatisfactory treatment, the patient may be reluctant to continue with an obviously trial and error process For his part, it is not feasible for the physician to plead that there is no other way of determining the best drug

A bad initial impression of a drug often leads to enduring and unshakable prejudice and causes the physician to avoid using it in situations in which it is eminently useful and safe Nothing is more likely to lead to a bad first impression than ignorance of uses, limitations, and dangers, and, conversely, nothing is more likely to lead to appropriate first impressions of new drugs than the knowledge which enables the physician to select the best drug for the therapeutic target, that is to say, the *drug of choice* Yet there is almost nowhere for the physician to turn for the kind of help he needs, certainly no place where unbiased, authoritative, and definitive information bearing on this problem is brought together and made easily available This volume is designed to satisfy this need by bringing together knowledge which is presently spread through the various specialties and, if published at all, published separately

It is a volume of expert *opinion* designed to provide the American physician with a comprehensive source of clear, concise, authoritative, and practical answers to the continually recurring question of which drug in a rapidly changing scene is, at the critical moment, the drug of choice for an actual therapeutic problem Many experts and educators in medicine have participated in the preparation of this book

Each was requested to express his own *opinion* of the drugs in current use in his field, based on his specialized knowledge and experience Controversy was avoided because, to be fairly explored, *controversy must be considered in great detail Such* discussions in the usual format of the review article often leave the reader still seeking the clear and definitive answer This we wish to avoid Although the ex istence of controversy may be indicated, the issues will not be argued here since such argument would defeat our purpose

Each day the drug manufacturer bombards his target through the mails with a barrage of attractive and eminently readable but far from disinterested literature which he regularly follows up with the attack direct by his detail man Here, the physician has his troubles, for although he may know that the drug house is perhaps the least likely source of disinterested opinion on the choice of drugs, it is understandably difficult for him, without authoritative support, to stand firm against this well organized campaign

The physician who reads the literature will find that the early reports on new drugs tend to be sanguine, the possibilities for utility emphasized, and the limitations minimized, for otherwise there would seem to be no reason to write about or to introduce a new drug Too often, the first hopes are not borne out by later ex*perience and, at best, require considerable revision and modification Most drugs* need time and experience for final evaluation, it is the very rare exception to this rule which, like penicillin, from the very beginning can be established as both eminently useful and safe

Most chapters are divided into several major sections, each section contains a concise discussion of clinical conditions in which the drugs under consideration are used, a consideration of the several drugs, and the nature of the available data which make one or another the more desirable Each section also contains a view of what the future holds and what is lacking in drug therapy in the particular area Each section has a list of selected references which provided the data on which the opinions expressed are based

Many drugs have more than one action and more than one sphere of clinical application In each of these the same drug may be relatively more or less effec tive, more or less dangerous, more or less important Since relative utility may vary with the clinical application, the same drug may be discussed in several sections of the book While this also reduces cross reference to an endurable mini*mum, at the same time it provides a satisfactory* compromise between repetition and convenience Drug mixtures are not often considered, not only because their number, with variations on the same theme, is so great as to be overwhelming, but also because their unique virtues are elusive difficult to evaluate There are very few mixtures indeed whose effects cannot be duplicated by the separate use of the constituents where a special function is performed by a mixture, it is here con sidered Biologicals are not considered since they do not fall within the scope of this book

Finally following each chapter there is an extensive but not necessarily com plete alphabetically arranged Drug Index of the drugs commonly used for the disturbances under consideration, including a capsule account of the drug, the

dosage forms in which it is available, and, as far as practical, their proprietary names and fabricators

The Drug Indexes have been compiled by the editorial staff, therefore, the Drug Index *will not help the reader make his choice* Recommendations of authors are to be found only in the text itself The Drug Index is an up to-date and representative list of drugs in common use, limited in size by practical considerations Many obsolete and obviously irrational medicaments have been excluded, but many drugs with limited utility are included simply because they are still being used When the number of proprietary names for a single drug was so large as to make their complete listing a stupendous as well as an entirely unrewarding undertaking, many of the proprietary names were omitted Even so, the Drug Index for some chapters may seem overwhelmingly long Where this is so, it is merely a reflection of the situation which confronts the practicing physician every time he is faced with the problem of choosing a drug in that area

There are instances in which the drugs listed in the Drug Index are not mentioned in the text It should be assumed that the use of these drugs is not recommended, that they are either of insufficient merit to warrant space and effort required for a statement, or, as in the case of new and untried drugs, that at the time of the writing there were insufficient clinical data available for a definite opinion on their utility

There is no indication that the present birth rate of new drugs will diminish, no likelihood that a moratorium will be called Complicating matters still further is the fact that many new drugs are still being explored for yet more suggestive actions and, as in the case of the phenothiazine compounds which were recently introduced only for their antihistamine action, new therapeutic uses are being continually proposed It is to be expected, therefore, that the appearance of drugs and reports yet to come regarding accumulating experience with those already introduced will provide ample material for revision on a regular basis

The editor of any collaborative book, for the most part, exploits the authority, the knowledge, and the talents of others His only justification is the purpose and the value of the end product I would therefore, like to thank the eminent collaborators of *Drugs of Choice* None of them had the time to spare, they found the time because they agreed with me that such a book was needed I am grateful to Dr Margaret Garrett for her assistance in proofreading

I wish to thank Dr David P Barr for his encouragement when my part in the undertaking seemed beyond me I also wish to express my gratitude to the late Frank A Volk, of The C V Mosby Company, whose enthusiasm for the project was both gratifying and helpful I owe the Sydenham statement which opens the book to the kindness of Dr William B Bean

WALTER MODELL, M D

New York

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DRUGS OF

CHOICE 1960-1961

PRINCIPLES OF THE CHOICE OF DRUGS

Walter Modell, M D

INTRODUCTION

To judge whether a drug is useful in a specific clinical setting or, where there is more than one drug available to decide which is preferable requires two kinds of pharmacologic information (1) data obtained through studies in the laboratory and (2) data developed through studies in man

ESSENTIAL PHARMACOLOGIC INFORMATION

In the choice of a drug the laboratory investigations which supply information and the proper interpretation of the data they provide are basic because knowledge about the actions of a drug, its potency, and its toxic effects gives the initial clue to its therapeutic potential and its safe use Most of the important drugs in modern use have come by way of the laboratory, for example, penicillin, only a few old ones like digitalis, which came into medicine by way of an accident or the herb doctor, survive

Bearing of Experimental Data on Clinical Utility of Drugs

This is an appropriate place to make clear that there is no conflict between the data of the laboratory and the clinic If properly selected, laboratory findings are more often directly applicable to the clinical situation than many clinicians admit That a disparity should sometimes seem to exist generally arises through neglect of pertinent laboratory data or through their improper interpretation

Chemists and drug manufacturers have an understandable tendency to make assumptions of drug utility where there is only superficial evidence that clinical requisites are satisfied The newspapers too, especially the Sunday supplements, have a special passion for disclosing undigested information on drugs which have a suggestive design of pharmacologic action and for presenting them forthwith as having unquestioned clinical utility

Such publicity frequently is followed by public pressure on the medical profession to make premature use of poorly tested drugs More often than otherwise, trial of these drugs in man fails dismally to fulfill the unwarranted predictions made

for them or even remotely to satisfy the need for which they *appeared to be suitec* Too often, such failures are interpreted as evidence of lack of compatibility between laboratory data and clinical application and as implying that the forme are of limited utility in the evaluation of drugs for man

It is of the utmost importance to realize that it is the initial observation of th pharmacologic properties of new drugs in the laboratory animal which gives th clue to utility as well as makes possible their safe exploration in man Thus th *animal, the experiment, and, in fact, the pharmacology laboratory are basic to prog*ress in therapeutics

The pharmacologic properties of drugs as seen in the animal are likely t apply to man when laboratory experiments are carefully analyzed and applied onl to those clinical situations which really correspond Although species difference are sometimes very striking, it is often possible to avoid this disparity by the choice o the appropriate laboratory animal When appropriate associations are regularly made *there will be far less time and effort lost in the futile trial of drugs which do no* apply to the conditions for which they are tested The well designed laboratory investigation should provide precise information essential for determining the applicability of a drug to clinical problems, the physiologic functions altered by the drug, the nature of toxic reactions, and the likelihood of species differences in relation to drug tolerance as well as pharmacodynamic action

The nature and extent of the physiologic dysfunction in man to be rectified by therapy must be borne in mind and compared with that in the experimental animal in which the drug was tested, or a mismatch will inevitably result Notable examples of such mismatches can be cited Respiratory stimulation can be induced in the cat with several drugs, but it may not be automatically assumed that these drugs will stimulate clinical depression of respiration In fact, respiratory stimulants in clinical use do not produce the same striking stimulation of the depressed respiratory center seen in the laboratory animal That clinical depression of respiration continues despite *decreased oxygen and increased* carbon dioxide content of the blood, both excellent stimulants of the reactive center, is strong evidence that the respiratory center is not only depressed but also resistive to stimulation The reason why the respiratory analeptics now in use are disappointing is not that the respiratory center of the normal cat is different from that of man, but that the respiratory center examined in the laboratory is different from that in the clinical situation (see *Chapter 11*)

The pharmacologic actions of drugs can usually be trimmed down to very simple and precise terms since fundamentally drugs either stimulate or depress some physiologic function These include toxic and undesirable actions as well as potentially useful effects When drug actions seen in the animal are analyzed on such a basis, one can compare the experimental and clinical setting to decide whether there is sufficient similarity between them to hope for clinical utility A drug which anesthetizes a normal animal is very likely to anesthetize a patient because the physiologic setting in both is similar, e g, the central nervous system of the patient is usually as normal as that of the cat before the anesthesia The action of antidotes in the poisoned animal is also likely to correspond with that in man because the type of action called for and the setting are much the same in both

NCIPLES OF THE CHOICE OF DRUGS

There are, of course, instances of disease or dysfunction in man for which ere is no laboratory duplicate against which to test a drug However, when the inical situations with their physiologic dysfunctions are carefully evaluated, com arable laboratory-induced states in animals are usually possible Sometimes the ssociation between laboratory and clinical states can be made out of piecemeal onsideration of the disturbance in man Where it is a fact that there is no labora-tory counterpart, the deficiency on the part of the laboratory must be reckoned with, and in such a case it may be that only evaluation in the patient will provide information on clinical utility In any event, a careful and precise analysis of the disturbance caused by disease as well as that of the situation in which a drug is ex amined is essential if the findings in the latter are to be applicable to the needs of the former

The Nature of Chemical Relationships of Drugs to Clinical Use

Our understanding of structure activity relationships of many drugs has pro-gressed to a point where the pharmacologist can often design a chemical structure and predict its pharmacologic action and toxic effects with amazing assurance The genius of the synthetic chemist is such that he plies the pharmacologist with new drugs with interesting and challenging actions His ability to make these new drugs threatens our present capacity for their careful clinical evaluation

In considering new drugs, knowledge of previously investigated congeners is important as a basis for speculation and prognostication It is equally important to recall that new drugs may or may not have all the particularized actions of the mother substance, in the transformation, they may have lost some facets of action or gained entirely new ones It is important to recognize that some new drugs are inferior to the old ones which they were supposed to displace, alterations are not invariably improvements Despite our highly developed talent for predicting the pharmacologic actions of freshly synthesized drugs, only examination in the animal and long trial in man tell the complete story Sometimes the full potential for harm as well as the limit of utility is realized only after two or three years of clinical use

Patterns of Drug Action

The parameters of drug action provide the practical considerations whi determine whether a drug with an attractive pharmacodynamic design will prove u ful Potency, curve of action, characteristics of absorption, elimination, all p a decisive role in determining where a drug may be used and, in the end, wheth despite eminently desirable pharmacologic actions, it can be used well or at This is to say, not only are pharmacodynamic effects important, but even w drugs possess the most desirable of actions, administration by an acceptable r in the circumstances which exist must be feasible and the desired effects mu producible within an acceptable period and maintainable at a desirable lev ful period of time Well-tailored pharmacodynamic ac enough and last long enough T

Potency —The potency of a drug, namely, the amount by weight necessary to produce an effect, is of obvious practical importance since it determines the absolute amount which will have to be given to induce an effect, but beyond this it is not a very telling bit of information *Provided it is possible to produce equal* intensity of effects with other drugs, absolute potency per se is not an outstanding determinant in drug choice For example, since it is possible to reproduce all the effects of 1 mg of digitoxin on the heart with digitalis leaf, which is 1/1 000 as potent merely by giving a 1 Gm dose, *the difference in absolute potency provides* in itself no basis for a choice between them

In some instances, potency of drugs is so expressed in the literature as to become truly misleading For example, there are barbiturate drugs for which the average hypnotic dose for man is appreciably smaller than that of the usual barbiturate less than the common capsule containing 100 mg Such a barbiturate has been advertised as being safer than others of which more has to be used for similar effect The implication here is that the smaller absolute dose is less likely to cause difficulties On the other hand less potent barbiturates which require more drug per hypnotic dose than the usual 100 mg have been advertised as being preferable because a larger than usual amount is required for toxic effects The *implication here is that difficulties are not so likely to be encountered because a* larger than usual amount of drug is needed to cause toxicity Obviously, both arguments cannot be correct but what is more important is that *both are wrong* Yet the fallacies in these cynical claims have escaped many, and few are sensitive to the fact that relative potency is not nearly as important as relative difference in therapeutic ratio

Relative potency has more meaning when it implies that more can be accomplished with one drug than another that is to say, when one drug has a higher ceiling of action than another Thus even though both drugs have qualitatively similar actions on the heart it is possible to produce effects on the heart with quinidine which cannot be duplicated with any dose of quinine It is the higher *ceiling of action of quinidine that makes it more potent than quinine in cardiac* arrhythmias not the difference in absolute dosage required to duplicate some effects

Untoward Reactions —There are two categories of untoward reactions (1) those which can be related to dosage and to a large extent anticipated i e, toxic reactions and (2) those caused by infinitesimal doses and largely unpredictable i e allergic reactions

Toxic Reactions —It is a characteristic of the clinically safer drugs that there is not only a reasonably predictable toxic dose but also that before this is reached *there is a range in which such reactions are rare* and when they do occur, are not serious Larger doses of course tend to produce both a higher incidence of toxic reactions and more intense or serious reactions Finally, there is a dosage range in *which serious reaction or fatality may be anticipated*

Often the aim of new additions to a series of related drugs is to reduce relative toxicity by the chemical alteration The ancestry of the drug is highly suggestive of what the possibilities are and *until experience proves otherwise, knowledge of* toxic reactions which have occurred with one member should be taken to indicate that such a potential resides in new and related members of the same group of

gs For example, Nirvanol, a hydantoinate which was used many years ago in gland for chorea, was followed so regularly by fever and a skin eruption that s reaction, called Nirvanol sickness was literally a part of treatment and with- t it therapeutic effects were not anticipated It was to be expected, therefore at in another hydantoinate Dilantin introduced many years later, there would be similar toxic potential The reason that Nirvanol was discarded and Dilantin has ontinued in clinical use is that the differences in structure though small ignificantly separate the anticonvulsant and toxic effects Dilantin can usually be employed without untoward effects, but it is equally noteworthy that the change in chemical structure did not entirely eliminate the reactions On the other hand, it has been shown that Mesantoin another congener of Nirvanol, produces its pharmacologic effects through biotransformation to Nirvanol It is not surprising, therefore, that they should be similar toxicologically as well as therapeutically

Unfortunately, statistical expressions of toxicity and safety with drugs do not necessarily apply to the individual he may deviate markedly from the average patient For him, only careful observation will supply the necessary safeguard against serious reaction An especially useful characteristic of some drugs, e g the digitalis glycosides, is the well timed development of minor toxic symptoms they should never be considered as they are by some a nuisance When they appear they serve as a clear warning that further administration of the drug to a particular patient may end in disaster while prompt cessation will be relatively uneventful On the other hand drugs like the coumarin anticoagulants which produce few if any minor toxic symptoms and whose first reactions are relatively serious ones, are treacherous regardless of therapeutic ratio because they fail to provide a warning that poisoning is developing

ALLERGIC REACTIONS —Allergic reactions may develop without warning Some drugs, however have earned a reputation for a high order of allergenicity and these and new ones of the same series should be treated with due considera tion for this propensity

Too often there is no way of testing for such a potential in a particular drug A history of allergic reaction to an older drug in a particular patient is a stron suggestion to proceed with caution with related drugs A tainted heredity i patient as well as drug should never be ignored

The Curve of Action —This is the curve of intensity of pharmacologic acti of a drug described during its development maintenance, and dissipation It is great practical importance in the choice and the regimen of use of drugs, it i capsule account of how long it takes for effects to develop and how long they p sist It indicates whether a drug may or may not be useful for emergencie maintenance It provides the information basic to dosage scheduling Its con nents should therefore be examined The development of drug action in the depends on several aspects of absorption rate extent and site of administrati

RATE OF ABSORPTION —The rate of absorption determines when a drug be pharmacologic action at the site of its action Rate of absorption when after administration a concentration de le, to say nothing of a useful, on must pro

very rapid absorption or by intravenous injection circumvent the process of absorption entirely On the other hand, where slow development of action is acceptable, the rate of absorption is a matter of less importance in the choice of drugs

EXTENT OF ABSORPTION —The extent of absorption is important in relation to the amount of drug that must be administered as well as in the choice of a drug Obviously, where a drug is completely absorbed from the gastrointestinal tract as in the case of digitoxin absorption is not a factor in the choice, whereas ouabain, which is not absorbed from the gastrointestinal tract, would never be chosen for oral administration The extent of absorption relates to the dosage necessary to produce desired effects Dosage of poorly absorbed drug has to be large enough to make up for the proportion of the total which will not be absorbed Irregularity in absorption may make dosage uncertain and may even make the use of the drug unsafe

SITE OF ABSORPTION —The site of absorption is important in determining the suitability of drugs because (1) in a particular patient it may not be reasonable to expect absorption from the site of administration (e g, oral administration in a patient who is vomiting or subcutaneous administration in an area of massive edema) (2) the drug may be destroyed at the site of administration (e g, by gastric acid) before appreciable absorption can take place, (3) absorption may not develop rapidly enough at the site of administration

INTERMEDIARY PROCESSES—*There are many examples of latency in action* Digitoxin may be injected intravenously, yet even though all the drug appears immediately in the blood stream, many hours elapse before full development of action *Obviously, some intermediary process or processes are involved in such delayed drug* actions, these may include changes in the nature of the drug to prepare it for its action cellular penetration development of secondary reactions, and others This *fact is of practical importance because, if unexpected results due to cumulation are* to be avoided, sufficient time must elapse between one dose and another to permit full development of action To the extent that these processes delay the development *of action, they influence the curve of drug action*, the routine of dosage, and the choice of drugs

ELIMINATION —Once a drug appears in the blood stream by whatever means of absorption or from whatever site, processes of elimination begin Sometimes these operate in force almost at once so that, as in the case of epinephrine, if a dose is injected intravenously slowly, the peak effect may be appreciably lower than when the same dose is injected rapidly Similarly, drugs absorbed very slowly in the intestinal tract, or whose absorption is retarded by food or some deliberate device, may also lose effectiveness On the other hand digitoxin is excreted so slowly that elimination does not significantly alter the development of the curve of action

The means by which the effects of drugs are dissipated are varied and are not known for all drugs Some are destroyed or altered in the body, some are eliminated either unaltered or changed in the urine, some in the feces, some by expiration It is conceivable that serious defects in an organ of elimination may alter the curve of action by delaying elimination However, significant deviations from the usual curve of action for particular drugs are usually caused only by far-advanced disease of the organ of elimination *Characteristic deviations* of this kind have been used for diagnostic tests but are also the basis for the choice of drugs

The Therapeutic Ratio—The physical amount of a drug which will produce a pharmacodynamic effect has special significance in relation to the amount of the same drug which will produce untoward effects under the same circumstances, for its ultimate usefulness in clinical medicine probably depends on its therapeutic ratio the relationship between therapeutic and toxic potency Whether or not a drug is safe as well as useful depends largely on how well these two categories of drug action can be segregated in terms of dosage

The therapeutic ratio is a far more realistic indicator of drug safety and utility than absolute potency or absolute toxicity For the therapist, it weighs the effects he seeks against the untoward reactions he fears It is a mathematic expression of this therapeutic attitude becoming more favorable as the gap between the therapeutic effectiveness and toxicity widens

It is interesting that in the case of the barbiturate drugs the therapeutic ratio is virtually the same for all members of this large series of drugs, the more potent as well as the weaker members This is to say, as much more is required of the weaker barbiturates for therapeutic effects as for toxic effects and, conversely, in the case of the more potent barbiturates, proportionately smaller amounts are required for both toxic and therapeutic effects, therefore, there are no barbiturates which have advantages in terms of relative safety Their important and realistic differences lie in other aspects of their parameters of action Uniformity of the therapeutic ratio in a series of congeners applies to some groups but is by no means invariable When chemical changes bring about significant improvements in the therapeutic ratio, they provide us with safer new drugs But there are other possibilities in the case of new drugs absolute potency may rise or fall, absolute toxicity may rise or fall, new facets of action, therapeutic or toxic, may appear or old ones may disappear the therapeutic ratio may fall or remain unchanged new drugs are not necessarily superior to the old and they may be worse—one has to find out which in each case

Dosage

It is the opinion of outstanding therapists that improper dosage with the proper drug is at least as common a reason for therapeutic failure as the application of an improper drug Token effects of drugs are useless, while enthusiasm as the only governor of the dosage regimen leads to disaster

Dosage may be insufficient through the physician's timidity or the patient's tolerance, excessive through the physician's exuberance or the patient's sensitivity To obtain from a drug all that it may provide, the dosage must be tailored to suit the patient as well as his disease Dosage is an individual matter depending not only on the potency and toxicity of the drug, but also on the urgency of the condition, the mode of elimination of the drug, the influence of the patient's disease on reactivity and elimination, whether the effect desired is to be sustained, intermittent, or occasional, and the physical inconvenience of repeated dosing where sustained effects are desired Finally, there is an unpredictable and to a large extent an incalculable factor—the patient's constitutional tolerance or hypersensitivity to the drug—which plays a vital role in determining safety as well as dosage for him but which can be estimated only after he is exposed to the drug

As already indicated the dose of a drug which may be used *implies a con sideration* of the amount necessary to induce a useful therapeutic effect in the face of the danger of inducing untoward effects on the one hand, and, on the other, that of failing to relieve the condition *in good time* *The probability of the therapeutic* utility of a dosage scheme depends on the nature of its compromise between safety and pharmacologic action

The Average Dose—This term is *really* a misnomer and is not what it seems to *mean*—a *mathematic* average of all the doses given, rather it is the dose given the average patient As it is now used, it usually signifies the probably safe dose with which to start the trial with the drug in the usual patient Actually, it is a dose calculated to induce a relatively low incidence of untoward effects in an un tested patient and burdened by this limitation, a practical probability of useful effects

The ratio between the two is variable, depending on the nature of the drug True toxic (not including allergic) reactions to penicillin occur very rarely An extremely large number of units (25,000,000 in some cases) have been given with out untoward effect As a result, the average dose of penicillin tends to be gen erous and is likely *to be followed by a very high incidence of satisfactory results* Another antibiotic streptomycin, may be followed by about 10 to 15 per cent of vestibular disturbances In this case, the average dose with an eye fixed on toxic *effects, tends to be conservative and as a consequence, the average dose of strep*-tomycin is not as frequently effective as the average dose of penicillin

Dosage Schedule—The dosage schedule is just as important as the individual dose because it has the same potential for making treatment either ineffectual or excessive If it provides the drug faster than the patient can excrete or destroy it, regardless of how small the individual dose may be, excessive effects will eventually develop If it supplies the drug slowly so that the patient eliminates it faster than it can cumulate a therapeutic level may never be achieved Thus, depending on the need and the way a drug is administered, cumulation and failure to cumulate can both be either desirable or disastrous

The duration of effects provided by the dosage schedule will often determine the success with a drug When the patient requires continued drug action, as the patient with heart failure requires digitalis a system of dosage must be provided to supply this need On the other hand, in the patient with episodic asthmatic at tacks, continued epinephrine action might end in disaster while occasional use may add up to therapeutic success

Potency as a Basis of the Choice of a Drug—It has already been stated that *absolute potency, hence absolute dosage*, is not as important as biologic potency and biologic dosage in terms of what can be expected from a drug What a drug will accomplish is obviously more significant than how much, by weight, is needed to *do it* *What real difference does it make* if one can accomplish precisely the same thing with twice as much of one drug as another? In a sense, the now almost completely outmoded system of unitage has advantages over the absolute doses we use *for our highly purified drugs* *It is a dynamic* method and has implications of dose effect relationships not inherent in the absolute dosage system

Another consideration relating to dosage which has a high priority rating in

determining choice is the therapeutic ratio This contains the answer to the question whether one drug or another used in the way dictated by biologic potency, pharmacologic actions, and the clinical condition is the safer

The parameters of its action indicate precisely how a drug has to be manipulated to induce and sustain a particular pharmacologic effect, that is to say, the route of administration, the size of the individual dose, and the dosage regimen The difficulties which attend this accomplishment in the case of one drug as compared with another are important practical elements in the choice between them

PRINCIPLES IN DRUG EVALUATION

It is a shopworn medical maxim usually blandly stated with little thought for its implications that "each new patient is yet another experiment in therapy" It should be so, of course, but rarely is more than lip service paid this statement

The clinical experiment involves a rigorous discipline and for proper performance sometimes demands even more skill, insight, knowledge, and, above all, patience than the proper laboratory experiment The discussion of the principles of the clinical experiment which follows may be useful to the practicing physician, not so much as the basis of his evaluations of new drugs as for the examination of reports on new drugs

The program for the evaluation of the clinical effects of drugs must be designed in such a way as to eliminate or take account of all forces other than the drug itself which may influence the response to treatment This involves (1) the resolution of forces extraneous to issues at hand, (2) the resolution of psychic factors in the response to medical care (3) the selection of the proper subjects for the evaluation, (4) the selection of the proper dosage for the evaluation of the drug under consideration, (5) the utilization of appropriate controls, (6) the determination of the sensitivity of the method, and (7) the selection of the best method for the collection of data Data collected with these precautions must then be subjected to analysis, often statistical, to determine their significance

Resolution of External Forces—The resolution of external forces deals with such diverse influences on the state of the patient's well-being as the course of his illness, changes in weather, and the turn of world affairs All may affect the responses of a patient to an inquiry regarding his reaction to treatment, for all may influence his physical well being as well as his sense of well-being Since these are chance occurrences the possibility that they may influence results may be eliminated through the randomization of medication This implies that in clinical evaluation some control has to be used to provide a basis for comparison—another active drug and, preferably, also a placebo

Resolution of Psychic Forces—The importance of psychic forces on the course of disease has been stressed mercilessly in recent literature The patient's desire to get well and his response to the fact that he is receiving accredited attention and reassurance—the so-called placebo effects of treatment—tend to provide the illusion of effects from medication itself and to make it difficult to distinguish the difference between the specific effects of the medication and the inevitable nonspecific effects of the fact of receiving treatment, that is, the placebo effect inherent

ment Sometimes the distinction can be made only after long study, prolonged periods of treatment, and large numbers of properly controlled comparisons

Confronted with reports of good and even dramatic results from new drugs, it is well to recall that dramatic cures have been reported after the ministrations of modern as well as ancient witch doctors, Christian Scientists naturopaths and a Canadian twist of the foot by Dr Locke Think also of the regimens which were once espoused by the medical profession which, like the protein hydrolysates for peptic ulcer, are now somewhere in limbo while the peptic ulcer still awaits satis factory medical treatment

RESOLUTION OF UNCONTROLLABLE BIAS —The attitude of the physician as well as of the patient is important in shaping responses to treatment Both are usually hopeful they desire that the medication do the job

The physician wants to do good because that is his function in life His recent experience with such new drugs as the antibiotics, cortisone, and anticonvulsants has given him a realistic basis for an optimistic attitude toward new medication The patient is usually hopeful for more selfish but nonetheless persuasive reasons On the other hand, there are patients who for reasons of their own want to suffer, to remain invalids, to receive special attention This attitude may induce negative responses to medication

The physician's knowledge of the medication he is prescribing is exceedingly important in the clinical experiment, for, regardless of how much he tries if he knows what he is prescribing, in one way or another he will communicate his feel ings about the medication to the patient If he has deep concern over the unto ward possibilities of the new and poorly understood medication he is using he will communicate his concern to the patient, if he is bursting with enthusiasm, he will communicate this attitude It has been shown that knowledge of participation in an experiment also distorts patient response, subjects who know they are being ob served often tend to be tolerant to discomforts

How to deal with bias is one of the great problems of the discipline of drug evaluation It would appear to be a practical impossibility for the practicing physi cian because he cannot and should not be blind to the medication he is giving his patients He writes his own prescriptions and must know what danger signals to look for In the clinical evaluations of drugs, ignorance of the medicament pro vides a useful way of eliminating bias, for getting at the truth A well recognized procedure is to make placebo and medication identical in appearance to use both but to keep physician and patient ignorant of what is in use both at the time it is prescribed and when the patient is being questioned This has been aptly called the double blind procedure

THE DOUBLE BLIND AND THE ALL-BLIND —Much has been written in recent years about the double blind technique It is my stand that while the technique must be applied in virtually all instances of drug evaluations in man, the blindness must begin and end at the proper time and that double blindness does not ensure valid results in otherwise poorly designed studies, and, in general that it is no cure for myopia or astigmatism in drug evaluation

Double blindness is nothing more than one device in the methodology of study ing drugs in man, it is not a complete method in its own right This is an im

portant practical matter, for the application of the double-blind technique has been used to whitewash otherwise seriously deficient methods of drug evaluation The double blind procedure has been mentioned in the titles of papers as if its use *proved the validity of the conclusions Nothing could be further from the truth* It merely ensures the removal of bias and identifies placebo forces in shaping responses, in no way does it guarantee that the data so accumulated are otherwise untainted and can be used for definitive conclusions without further analysis

Appropriate Subjects —The argument that the patient for whom the medication is intended is the best subject for its evaluation seems to be a truism Yet there are situations in which he might make the worst subject for drug evaluation For example, the very suggestive patient with anxiety symptoms may react with such wide swings to both placebo and treatment as to make it utterly impossible to demonstrate differences between sedative and placebo actions On the other hand, because of the highly specific nature of the drug action which relieves it without producing serious central depression the influence of drugs on myalgia can only be studied in patients who experience it spontaneously

Highly suggestive, very labile and very phlegmatic patients, patients who have such high regard for the physician that they try to show their appreciation for his efforts by responding positively to all he does and, conversely, those who feel that only by overstating their case will they get full value from their physicians make poor subjects and tend to reduce the sensitivity of methods used in the evaluation of drugs The proper subject for an evaluation varies with the type of drug effect under examination, the nature of the dysfunction to be influenced by the drug, and the sensitivity of the method necessary to demonstrate a drug action in man

Appropriate Dosage —If dosage is too low regardless of the pharmacologic actions of a drug, clinical evaluation in man will reveal no difference between the drug and placebo, dosage so high as to produce undesirable effects may obscure therapeutic merit and discourage further examination of the drug A body of previous experience with the drugs as well as its congeners, often in the form of a pilot study, must be used as a basis of ensuring the use of the best dose or series of doses for the evaluation There is no such thing as an evaluation of a drug without a control, for a control is merely a basis of comparison, and therefore, every statement about a drug implies a control Consequently, there are no uncontrolled studies merely studies with appropriate controls and studies with inappropriate controls

Appropriate Controls —In the animal littermates provide the classic controls so that sex, age, weight, as well as constitutional features are identical in treated and control animals All that is required is the proper purchase order to get quantity as well as *quality in control* This is not the case in the clinical *experiment* The identical twin who serves as a control for his brother is a once in a lifetime coincidence If alternate cases are used for control the treated patient may be a young thin bachelor and the alternate patient an obese elderly woman who has borne a dozen offspring They may come from different economic and cultural environments The influence of these differences on the effects seen and reported after treatment may be enormous Satisfactory matches for purposes of control are rarely available and only large numbers suffice as a substitute The subject may serve as his own control by alternating periods of treatment with periods of placebo

medication But this procedure must be carefully scrutinized, since the patient s illness may change in such a way during the study as to shape the results

Yet, since no valid comparison can be made without them, appropriate controls must somehow be provided Where a large number of patients are available, alternate cases are likely to equalize the effects of extraneous influences and may, therefore, be used for control Where patients are few in number, the only recourse is to have each patient serve as his own control through the use of both drug and placebo in each case With randomization of medications and a sufficient number of trials in each patient, it is often possible to rule out progression of disease as an influence in the total response of the patient to treatment For experimental use no control is more precarious than the so-called 'historic control that is a recollection of previous experience Yet in the case of exceedingly rare diseases this may be the only control possible and it is also the basis of the physician s own method of accumulating experiential knowledge

Collection of the Data —The collection of data is a critical matter in all scientific investigations Here the training skills, and acuity of the scientist are of first importance In some studies in medicine, observations can be made by objective clinical findings, x ray, electrocardiogram, changes in temperature, weight and other means When they reflect the action of drugs, such data simplify the problems in drug evaluation Unfortunately, not all drug effects can be measured directly Many drugs are used for the relief of symptoms, and their effects, as expressed by the subjective responses of patients, are not so easily reduced to objective data as clinical responses which can be recorded by x-ray or thermometer

In the evaluation of drugs influencing the pain experience, for example, the patient is the only observer of the effectiveness of the treatment There are many other areas of drug evaluation in which the patient's subjective experiences must be used as the basis of measuring the differences between the actions of drugs The difficulties in collecting responsible data may profoundly influence the method as well as the validity of the conclusions the data seem to indicate

The patient is asked to recount his experiences, evaluate them, eliminate extraneous forces and wipe out his bias and his desire to get better or worse He is asked to obliterate the total effect of all these influences during the period of treatment from the effects of the medication itself There are few scientific investigations in which so critical a part as the collection, storage, and interpretation of observations is left in the hands of an interested, biased and untrained assistant—in this case, the subject himself

Responses to treatment should be collected immediately after the experience Unfortunately this is not always possible Yet, if the subject has to wait before reporting matters may be further confused, for he cannot help having his recollections colored by more recent events than by those farther back—what happened two days ago against two hours ago Report cards which the patients fill out every night summarizing the day's experience have a theoretic advantage over responses gathered after longer periods of treatment Postal cards which patients mail to the physician every night are still better because they provide assurance that the card was filled out at the end of the day stated In order to ensure fresh and uncolored responses it has been found advantageous in some studies to question the subjects by phone each night The most accurate data are those accumulated by an on the-

spot observer This, however, imposes a heavy burden on those who are ev drugs in man

Sensitivity of Method—Devices for measurement must always be eva to make certain they have the requisite ability to discriminate The physic satisfied with the examining room scales to weigh a patient, but the chemist on an analytic balance which is sensitive to differences of fractions of milligr The same is true in clinical evaluations The method itself must, in fact, be pro if it is to be fairly stated that the results it yields are reliable The ability o method of drug evaluation to distinguish positive from negative or indiffer responses can be established by demonstrating positive responses with drugs known activity Sensitivity can be shown by the increments in dosage which th method can distinguish

Statistical Significance—Often one reads that a difference was found but i was not proved to be significant or that there was a trend which was not signifi cant This is an unworthy way of approaching data Only significant data have merit and nonsignificant data may not be used to suggest a possibility If a dif ference is not significant it is not a real difference and regardless of qualification should not be stated as one

Because of great variability in disease expression to individual differences, and to influences of extraneous forces the proof of the conclusions in drug evaluation often must rest on a statistical demonstration Great difficulties often attend the accumulation of adequate numbers of cases especially of the more unusual diseases Only statistical analysis can indicate the validity of the significance of differences found in data and the likelihood that they can be reproduced in the patient who receives the drug for therapy

The most efficient way to design a study for clinical evaluation is to deal with statistical problems at the outset to apply a method which can be predicted to sup ply valid data with the amount of material available the type of control which, for want of better may have to be used and the method of collecting data to which the physician is reduced Failure to take account of this problem in the design often ends with mountains of data which do not answer the questions posed

It cannot be gainsaid that the statistician has come into the act The details f his designs are often highly technical matters it is my practice therefore, to con lt a statistician at the beginning of a study as well as at its conclusion Statistical alysis however, does not examine the data itself It merely examines differences icated by the data Statistical prognostication is based on the assumption that data used were worthy of collection It must be emphasized, therefore that rdless of statistical considerations in all other aspects the design of the method also be such that it ensures the quality of the data Without the latter the tical analysis may well provide statistically significant but nonetheless erro conclusions

Interpretation of the Data.*—It is convenient to consider the design of a udy for clinical evaluation in terms of a balance which is used to weigh the evi nce for or against a particular pharmacodynamic or therapeutic effect of a d

he d scussion on Interpretation of the Data is quoted w nd Houde, R W J A M A 167 2090 195

as compared with chance occurrence Which way the balance swings, i e, whether drug action is favored or not, depends, of course, on the relative weight of the evidence in one or the other pan Whether the swing is meaningful or misleading depends on whether the weight which swings it is due to a specific action of the drug or to any of a myriad of forces which influence man's behavior and his mental, physical, and visceral activity When such a model is used, one way to prevent swings of the balance by factors other than the intrinsic pharmacodynamic action of the drug itself is to accept and spread their influence equally on both sides of the balance, thereby causing no disturbance in balance by their weight This is precisely what is attempted by the control devices of double blindness and *randomization they merely prevent chance and erroneous swings of the balance*

What is not often taken into account in clinical evaluations is how much weight is necessary to make the balance swing at all, that is, the basic sensitivity of the method Whatever the original sensitivity, consider what is done with it in the usual design for clinical evaluation Consider that such a balance is not empty at the outset of the evaluation, merely in balance on both sides of the balance one places equally placebo action of drugs, bias, and influence of diverse extraneous factors, such as weather, political events, family stresses, and a number of other vagaries of human experience that tend to mold or alter man's functional state and his response to drugs It is to be emphasized that these are not removed as interferences they are permitted to remain They are merely spread equally over both pans of the balance by the process of randomization and by the control of double blindness The balance is thereby deadweighted with a large amount of material which is immaterial to the specific problem at hand No matter how sensitive originally, such a procedure makes the balance less sensitive, just as an analytic balance, sensitive to a fraction of a milligram under usual conditions, is no longer swung out of balance by milligrams when dead weighted with several kilograms on each pan (Fig 1)

Ultimately, therefore, the sensitivity of a method of clinical evaluation is a *function of the relative weight of the pharmacodynamic force* under investigation and the weight of the nonessential interfering forces which are treated by equalizing them the greater the former with respect to the latter, the more sensitive the method, and, vice versa, when the latter becomes relatively heavier, the method becomes proportionately less sensitive The extent to which dead weighting the *balance grossly desensitizes the balance can lead to erroneous interpretations* in the sense that the balance indicates no differences whenever it is used to weigh what it is no longer competent to detect

Of the factors already discussed, some are subject to choice, such as the proper dosage range and subjects and the appropriate control Other factors may be modified The removal of the patient *from the home to a constant environment* in the hospital may sometimes reduce the extraneous variables The collection of data on the spot, *rather than placing it in the hands of the subject himself*, reduces the treachery of patient recall Finally, there remain some irreducible disturbances which can be neither removed nor modified, that is bias placebo actions, and the residual extraneous forces For these there *remain the double blind control and* the process of randomization to spread the prejudicial factors equally, so that none of them swings the balance in either direction

HOW TO SELECT THE BEST DRUG

By some means or other, the practicing physician must decide which of the drugs available or suggested for a particular purpose is the best It is his obligation to make this decision, but in doing so he must be wary of the prejudiced advice *served to him by the drug manufacturer* He is again advised that the drug

manufacturer will tell him little but the superiority of his product For e... there is a large volume on an antibiotic published by its manufacturer in wh... expression "untoward effects" and the word "toxicity" do not appear at all

He must listen to unbiased voices as well as try to make substantial esti... of drug utility on his own Many fine, original, even classic observations have made by the physician in the conduct of his regular practice Although they of great value, today they often cannot cover enough ground The busy practitio... rarely has the time or the opportunity to conduct the rigorous experiment in office or at the bedside and usually has to depend on the recommendations of experts he can trust The best source of such unbiased expert opinion is the med... cal literature

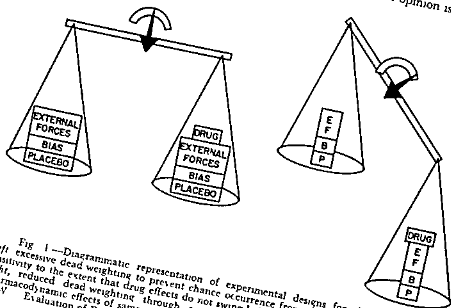


Fig 1—Diagrammatic representation of experimental designs for clinical evaluation *Left* excessive dead weighting to prevent chance occurrence from swinging the balance reduces ...ensitivity to the extent that drug effects do not swing balance and, hence, cannot be measured ...*ght*, reduced dead weighting through appropriate design makes it possible to measure ...harmacodynamic effects of same intensity with same balance (From Modell, W, and Houde, ... W Evaluation of Drugs J A M A 167 2090 1958)

In the literature the early papers on new drugs tend to give little compara... information, that is, in terms of superiority of particular drugs over others ...d in the same field It often happens that toxic propensities of a drug ...e to light only after considerable clinical experience The physician has to ... for the review article which usually is the best source of comparative infor... ...on Since there is a considerable delay between the introduction of drugs ...he publication of the review article, the physician is regularly faced with the ...m of considering a new drug about which he can get little definitive infor... How is he to come to a decision when the need is immediate? ...s always possible to find out from the drug manufacturer what the medica... ...ally is, the chemical structure, and the pharmacologic group to ... Experiences with older drugs in the same group ...

is likely to be a satisfactory literature on these related compounds which will provide information for prognostication Although the intent with new drugs is to eliminate or reduce the defects of the older relations genealogic studies of the older drugs usually have an important bearing on the new It is a good thing to bear in mind that a new drug *may not be better than the older one it is designed to replace* Sometimes it may even be worse

A new drug is never introduced on the American drug market without some publication in medical journals of studies of its pharmacologic properties, for without it the Government does not permit its sale While the drug manufacturer is unlikely to offer any unfavorable reports if nowhere else this reference may be obtained from him Information on some of the parameters of drug action is likely to be found here The ability of the parameters of action as well as the pharmacologic actions themselves to suit the therapeutic needs, and the characteristics of dosage form the basis of the choice of a drug, the basis for trying a new *drug in preference to continuing with the old*

Do not use a new drug in combination with other drugs no plan of investigation is more certain to obscure the merits or disadvantages of the new drug

THE CHOICE OF A PLACEBO

A word must be said about the choice of the ubiquitous medicament the placebo if only because there has been so much recent talk about it that clarification is necessary There is nothing really profound about it and it is just as old as the art of medicine There are two major areas for the use of the placebo the experiment and the patient

Placebo is used in the clinical experiment for a nontherapeutic function *to deal* with psychic responses in drug evaluation It is contrived and administered to duplicate in appearance and in mode of application the drug under investigation so that the subject does not know when medication is being switched In this way the physician may learn whether a particular form of therapy provides something more than placebo relief It may be used in general practice to determine whether the drug or the act of its administration is making the patient better—or worse

The second use of placebo is in treatment Many patients will have negative reactions to their visit to the physician if they do not come away with a prescription for medication such patients require and benefit from placebo Under these particular conditions *the placebo serves as a symbol of medical treatment* and is in fact treatment It may be given while waiting for the diagnosis essential to definitive treatment or even simply because the patient demands medication

The potency of placebo may be a blinding phenomenon The physician must be wary of the assumption that a strong positive placebo reaction provides a diagnosis of psychogenic origin or that a negative reaction to placebo proves the presence of organic disease Serious somatic disease may respond well to placebo while psychic distress may resist it *It should be an inviolate rule therefore not to permit the result with placebo to alter the routine of a thorough physical examination and a complete diagnostic work up*

Despite its effectiveness in particular instances, placebo should never be a substitute for rational medication and well considered therapy in addition to an equal

placebo effect, the latter will help in areas not touched by placebo, will produce more enduring results, and can cure where placebo cannot

In choosing a placebo, the physician has two choices the "pure," a tablet made of an inert material such as lactose, and the "impure," a harmless but inappropriate medication The most compelling argument against the former is that patients who have discovered the fact have interpreted it as dishonesty rather than treatment Since this interpretation harms the patient and threatens his relationship with his physician, there is an understandable tendency to use a placebo which the average patient cannot interpret as "dishonest"

I would argue endlessly that there is no taint of dishonesty in the well considered use of placebo, but I cannot gainsay the embarrassments of discovery The "impure" placebo eliminates them But if the patient becomes better after a polyvitamin capsule,* the temptation is great to attribute the results to the vitamins, however inappropriate they may be for the condition The "impure" placebo, therefore, threatens the physician's intellectual fortitude for he may be deluded that results are due to the *contents of the tablet* rather than the *act of taking the tablet*

I would argue also that the physician should always take pains to know when he is giving a placebo Only then will he make the fullest use of the placebo Only then will he be in a position to fashion the placebo which best suits the immediate needs and the attitudes of the patient to the physician and the taking of medication Only then can he decide whether the placebo should be solid or liquid, capsule or tablet, tasteless or repugnant, odorless or malodorous administered orally or by injection, given three times a day or once a week for maximum placebo effect

Beyond this accomplishment, when the physician uses the placebo expertly he will also be an accomplished and perceptive therapist, for he will be exploiting the only *universal medicament* as well as distinguishing the actions of others

SELECTED REFERENCES

Beecher Henry K Appraisal of Drugs Intended to Alter Subjective Responses, Symptoms, J A M A 158 399, 1955

Beecher, Henry K The Powerful Placebo, J A M A 159 1602, 1955

von Felsinger, John M, Lasagna, Louis, and Beecher, Henry K Drug-Induced Mood Changes in Man, J A M A 157 1113, 1955

Fischer H K, and Dlin, B M The Dynamics of Placebo Therapy, Am J M Sc 232 504, 1956

Gaddum, J H Clinical Pharmacology, Proc Roy Soc Med 47 11, 1954

Harris, S C, and Worley, R C Evaluation of a New Analgesic, J Appl Physiol 7 183, 1954

Jellinek, E M Clinical Tests on Comparative Effectiveness of Analgesic Drugs, Biometrics Bull 2 87, 1946

Lasagna Louis, Mosteller, Frederick, von Felsinger, John M, and Beecher, Henry K A [illegible]

Modell, [illegible]

Modell, [illegible]

Shapiro, [illegible] J A M A 160 30, 1956

Travell, Janet Assessment of Drugs for Therapeutic Efficacy, Am J Phys Med 34 129, 1955

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*It is of interest that even this placebo may be dangerous There are recent reports of serious consequences of the suppression of early signs of pernicious anemia by the small doses of antianemic materials in such mixtures

Chapter 2

THE PHYSICAL AND CHEMICAL CONSIDERATIONS IN THE CHOICE OF DRUGS

Lloyd C Miller, Ph D, and

Albert H Holland, Jr, M D.

INTRODUCTION

Physicians in the United States are offered a greater variety of forms of the same drugs than physicians anywhere else in the world This circumstance is a development of the keen and extensive competition under a free enterprise system in a highly diversified industry Although it is impossible for the busy practitioner to be intimately acquainted with the practical aspects of pharmaceutical chemistry, he should have some knowledge of the important physical and chemical characteristics of drugs that relate to any differences of significance upon which rests a basis for the choice of one form of a drug over another form of the same drug

The purity and composition of drugs is guaranteed in part by the standards set by *The United States Pharmacopeia, The National Formulary*, and *New and Nonofficial Drugs* Compliance with these standards is supervised to a degree limited by a small budget by the Food and Drug Administration of the Federal government However, in the case of such new drugs for which official standards have not been set by the U S P or N F, the reliability of the pharmaceutical manufacturer becomes an especially important matter When a drug is prescribed the reliability of the manufacturer is therefore at stake In addition, there may be two or more brands (with entirely different brand names) of the same drug How much good research quality control and effort does the manufacturer expend to protect the integrity of his line of merchandise? Brand named drugs carry the same implications of quality as brand named merchandise in other commercial fields This is of importance to the physician for he too assumes considerable responsibility when he prescribes a specific product

One cannot engage in a discussion of the meaning and importance of brand names without a consideration of patent rights There are some who view patents and patent rights as providing an unjustifiable monopoly, particularly so in the case of medicines The granting of a patent is a reward for the disclosure of an invention and provides the recipient with a protected period for profit

by exploiting his own invention Patent rights thereby provide motivation and incentive for originality and advancements which have contributed to the great progress made in the development of entirely new drugs as well as for more effective and more convenient forms of older ones

FACTORS INFLUENCING ORAL ABSORPTION

The remarkable extent to which chemical and physical factors can deprive patients especially the acutely ill of the benefits of medication is scantily appreciated Since the stomach is not primarily an organ of absorption, drugs must generally pass from it to the small intestine even to begin to undergo absorption This is particularly true of those drugs that are insoluble in acids, e g , the barbiturates Others are unstable in acid e g all of the penicillins except the phenoxymethyl derivative Thus prompt passage into the upper intestine favors absorption

However satisfactory passage from the stomach does not insure full absorption Indeed an extensive series of experiments has shown that for riboflavin, as a typical constituent of multivitamin tablets and for *p* aminosalicylic acid full absorption depends upon how promptly the constituent goes into solution This rather reasonable conclusion is not easily put to critical test but published evidence strongly suggests that plain tablets ought to disintegrate promptly after ingestion Thus there has been a sharp reduction in the disintegration time limits for tablets now allowed under the U S P standards as compared with earlier revisions This represents abandonment of the once prevailing concept that prompt disintegration is a virtue only for analgesics and other drugs needed for the fast relief" so freely promised in popular advertising

An argument held against short disintegration times when pharmacopeial limits were first imposed was that tablets tend to case harden on storage and failing the test would face discard Since the drug content was still up to standard there was little inclination on the part of manufacturers to regard this as simply another form of deterioration Yet when absorption is poor the patient obviously gets little benefit and the physician's plan of therapy goes awry

There is a recorded instance however of a small but ethical drug firm s having voluntarily recalled all outstanding stocks of a lot of simple uncoated sulfadiazine tablets that had become so hard as to pass through the entire gastrointestinal tract intact

The greatest risk is with special coatings and a recent study showed that a disturbingly high proportion of enteric coated tablets supplied on contract to a government hospital were excreted whole Fecal examinations in healthy students revealed that intact tablets or insoluble fragments were recovered up to 48 hours after ingestion The percentage of recovered tablets showed a high degree of correlation with prolonged in vitro disintegration by the U S P test for enteric coated tablets

These facts suggest that physicians ought to instruct the nursing personnel to look for excreted intact tablets when medication appears to fail or proves less effective than expected

Physiologic Availability of Liquid and Solid Dosage Forms—Among new drugs for use orally the solid forms outnumber the liquid 2 to 1 The greater convenience of the solid forms to patients is doubtless an important factor in their popularity However convenience may come, to an undetermined extent, at the expense of sure availability of the active ingredient A liquid medicine enters the fluid milieu of the stomach with no delay or loss beyond what may be adsorbed on the mucous membranes en route, in reaching and leaving the stomach It therefore is the form most available by mouth

Tablets and Capsules—New drugs for oral use are often first introduced in capsules for the pharmaceutic reason that thereby the problems of disintegration stability taste etc are bypassed Later, when solutions to these problems lead to suitable tablet forms the tablet forms are generally used because they are less costly to produce Despite this fact, capsules may still be continued if for no other reason than the fact that they lend themselves to closer identification with the maker by color coding banding or name imprinting The extra cost of this advantage to the producer is passed on to the patient

The hard shelled capsules are the most convenient form for extemporaneous dispensing by the pharmacist in filling prescriptions calling for sizes not available from the producer Generally the drug is not distributed in pure form without diluents so that the pharmacist may be obliged to crush regular tablets to a powder to fill the capsules Soft capsules require special machinery that forms and fills the capsule in a single operation

Capsule shells both hard and soft consist almost entirely of gelatin suitably plasticized These normally digest promptly in the stomach thereby making the capsule contents available for absorption only slightly less quickly than is a liquid medicament

Enteric Coated and Other Delayed Absorption Dosage Forms—The irritation to the gastric mucosa from readily soluble drugs taken by mouth is manifested by symptoms ranging from mild distress to severe vomiting Long ago this problem suggested finding a means of keeping the drug from dissolving until it had passed through the pylorus Though time honored, this approach merely begs the issue in being more nearly analogous to symptomatic relief than to outright cure It leaves unanswered the question of whether simply transporting the drug beyond the point where the patient feels or shows ill effects from the irritation is in keeping with the principle of *nolo nocere* (do no harm to the patient) Nevertheless the potential benefit from a simple drug such as ammonium chloride which causes intense irritation to the average stomach is sufficiently great to justify its use in a form intended to resist dissolution until it has reached the intestine

There are however other valid reasons for delaying the action of a drug until it has passed beyond the pylorus e g, to avoid its destruction by the acid of gastric juice or to protract the period of its absorption as a means of avoiding an exaggerated pharmacodynamic effect such as flushing of the skin produced by rapid absorption of nicotinic acid derivatives

Until recently the best means of achieving delayed absorption was by applying an enteric coating to a tablet or capsule These coatings consisted of acid in soluble alkali soluble substances such as various natural gums, waxes etc in

cluding shellac particularly and synthetics such as phenyl salicylate (salol) and cellulose acetate phthalate In general, these substances are quite insoluble in an acid milieu but are sufficiently soluble in the intestinal fluid to serve the intended purposes although, in fact, the latter fluid is never very strongly alkaline As stated by Dragstedt in 1958, the very number of these substances in use is "something of a mute testimonial to the fact that none has been found to be uniformly successful" [These include such proprietary preparations as Emplet, Encoat, Enerel, Enseal, Entertab, Keracote Ed]

Another pharmaceutic approach has been to use hygroscopic substances such as powdered elm bark and agar Incorporated in the coating of a tablet, these take up enough moisture from the stomach contents to initiate a disruptive process that proceeds slowly enough, in theory at least for the tablets to have passed out of the stomach before the coating breaks down

A fairly recent and promising development depends upon forming complexes of the drugs with ion-exchange resins Claims for these complexes include improved taste characteristics and increased stability The resins used are generally styrene divinylbenzene copolymers appropriately treated to create an affinity for either cations or anions Thus a cation exchange resin is used to complex amphetamine in such a way that the drug is released to its surroundings over an extended period of time The advantages claimed for these complexes include increased stability and greater certainty of action by circumventing most of the batch-to-batch variation that can occur in the application of enteric coatings In time, important economies in cost should be apparent However, as yet, production experience with the resin complexes is relatively limited

Physicians, in considering the use of delayed absorption dosage forms, should be aware that the difficulties faced by the pharmacist in making suitable delayed-absorption preparations are compounded by the physiologic variations normally observed in the emptying time of the human stomach [These include such proprietary preparations as Durabond Dura Tab, Extentab, Gradumet, Repetab, Spacetab, Spansule Ed]

Except for study made possible by such rare accidents as that which gave Beaumont the injured Alexis St Martin in 1819 long before full advantage could be taken of the opportunity, x ray examination has been the method of choice in following the fate of ingested medicine and tablets in particular Nearly always conducted on normal subjects, such studies have shown invariably that, because of individual variation, the time required for insoluble tablets to leave the stomach is remarkably unpredictable In some subjects all tablets taken have left the stomach within 30 minutes, while in others similar tablets are retained for hours, even after eating a full meal The pattern for any single individual is fairly reproducible

The popular belief that only liquids pass through the pyloric sphincter is, of course, untenable Fairly large tablets readily leave the stomach intact *provided* they are brought near the pylorus The force of gravity can be drawn upon to hasten passage from the stomach, especially if persons in bed are placed on their right sides In tests of this point, Gruber and his associates have shown that enteric-coated tablets passed out of the stomach quickly in each of several subjects

who turned on their right sides after having lain on the opposite sides for 6 hours, during which time the tablets remained in the lower curvature of the stomach Blood analysis confirmed the lack of absorption of the tablet contents Hence, for tablets that disintegrate but slowly or not until leaving the stomach, as is intended for those that are enteric coated, the tablet contents may be unavailable for hours

CHOICE BETWEEN FORMS OF THE SAME DRUG

The choice between two or more chemical forms of a drug depends upon both pharmaceutic expediency and the intended route of administration Few students of medicine can take time to inquire into the pharmaceutic aspects of organic chemistry and to inform themselves of the elements that profoundly influence the performance of the drugs they prescribe Therefore, they must rely upon the decisions made by others for pharmaceuticals provided in finished form

Simple Salts —Different salts of the same drug rarely differ pharmacologically, the differences are usually based on physical properties For physiologic as well as for chemical reasons, hydrochlorides are by far the most frequent choice of the *available salt forming inorganic radicals* For the same reasons, sodium *is the* most favored cation Of the drugs recognized in the U S P, the hydrochlorides outrank the sulfates the next nearest in frequency, nearly 4 to 1, and the sodium salts are in even greater preponderance The bromide and iodide salts are never chosen over the chloride except by necessity both because these halogens are not inert pharmacologically and because they are more expensive Ionic fluorine is used only in inorganic form as a specific prophylactic against dental caries, however, organically substituted in the structure of the drug principle, it may enhance pharmacologic activity remarkably

For pharmaceutic reasons, *the phosphate ion and various forms of sulfonates* are used, for example, methanedisulfonate, ethanedisulfonate, and camphorsulfonate The phosphate salts of the antimalaria drugs of the quinoline and acridine type were chosen because of better tolerance and greater efficacy after extensive comparisons in research conducted during the period from 1942 to 1946 as a military necessity The choice of organic acid radicals is dictated by chemical and pharmaceutic attributes Salt combinations with the monocarboxylic acids are generally insoluble in water and lend themselves to repository preparations Those of the dicarboxylic acids (above oxalic, which is too toxic to use) confer *water solubility if one of the carboxyl groups is left free,* a notable example is the water soluble hydrocortisone sodium succinate

Pharmaceutic chemists choose from the salts on the basis of convenience including cost of raw materials, ease of crystallization, stability, and such physical factors as hygroscopicity and flow characteristics of the resulting solid drug The pharmacologist takes into account elements of toxicity which lead him to select sodium over potassium and those organic radicals that are readily excreted or metabolized

For parenteral preparations, solubility and stability in solution are paramount *considerations,* and an objectionable taste poses no problem In contrast, for oral preparations, taste is important, and often a taste problem is eliminated by finding

a water insoluble form of the drug in question A good example is the antibiotic chloramphenicol, the hydrochloride of which is very soluble and bitter whereas the palmitate is so insoluble as to be tasteless

The Importance of Solubility—Solubility is relative, of course, and as the term is used here has reference to water and body fluids as the solvents The degree of solubility has important implications Codeine phosphate is sufficiently more soluble than the sulfate to be the form of choice for parenteral solutions This gives the phosphate an over all advantage, since it is equally suitable for all other applications, and accounts for its being the only salt of codeine recognized in the *United States Pharmacopeia*

The preparation of soluble derivatives of today's complex molecules severely taxes the ingenuity of the chemist who works with synthetics Where he has not yet succeeded, the pharmacist may be called upon to compromise as in the case of Mephyton Sterile Emulsion (sterile phytonadione emulsion, U S P) This is the only sterile oil in-water emulsion recognized for intravenous use The compromise was dictated by the need for a promptly effective form of this vitally important antidote to an overshooting of the mark in anticoagulant therapy More recently Konakion has appeared to provide the same drug dispersed finely enough in an aqueous medium to give the appearance of a true solution

The antibiotics and steroids which as a class are characterized by relatively large molecules, present several solubility problems Not the least of these have been the difficulties with tetracycline which is practically insoluble in water above pH 3 The synthesis of Syntetrin, a substituted tetracycline, N-(pyrrolidinomethyl) tetracycline, is welcome since the new derivative is 2,500 times more soluble than tetracycline at the pH of body fluids On the other hand, the relatively great solubility of the sodium and potassium salts of penicillin was a serious drawback because of rapid absorption from an injection site and prompt excretion This was overcome first by the discovery of the procaine salt which is soluble in water to the extent of only about 6 mg per milliliter Hundreds of other salts of simple and complex amine bases with penicillin have been prepared and examined of which benzathine penicillin and procaine penicillin have survived as the forms of choice for intramuscular use Modifications of the acidic moiety of penicillin have yielded phenoxymethyl penicillin, which has remarkable stability to acid and thus has advantages over benzyl penicillin The forms of penicillin recognized in the U S P include two distinct penicillin molecules phenoxymethyl penicillin and benzyl penicillin (penicillin G), the potassium salt of the former and four salts of the latter i e, sodium, potassium, procaine, and benzathine The sodium and the potassium salts are virtually indistinguishable, but each of the two other forms has attributes which give it distinctive advantages

Aerosol Mists—Pulmonary inhalation of drugs as a route of administration doubtless began with steam inhalation which is described in ancient medical records and is still useful However, with drug steam vapors, the particle size is seldom small enough for the drug to penetrate beyond the trachea Mists of particles 10 to 30 microns in radius that are obtained in "atomizers" may reach the bronchioles, but a reduction in radius to 3 to 10 microns is necessary to reach the alveolar sacs Such particles are attained by use of nebulizers based on the Venturi

principle of passing a jet of air or gas across the top of a vertical tube, generally of capillary bore, immersed in a solution of the medicament Making the jet stream of the drug solution impinge on a baffle subdivides the particles still further This form of medication has gained great impetus as the result of ready availability of suitable propellents, for example, the inert gases, argon and nitrogen, and the fluorohydrocarbons, such as Freon, which liquefy under low pressures This makes possible the modern form of aerosol packing of drugs that yield metered amounts of drug charged vapor on release Fairly accurate metering of single bursts of vapor is highly important in dosage control An additional attribute is the convenience of a compact, nonspillable package

Such risk as exists from overdosage in using the aerosol packages can be prevented only by educating the patient to limit the number of applications Responsibility for this should be assumed by both the physician, in prescribing, and the pharmacist, in dispensing the aerosol dosage forms

Comparative studies show that the cardiovascular side effects of isoproterenol hydrochloride are less following aerosol administration than after sublingual dosage, both of which compare favorably with subcutaneous injection The metered aerosols seem certain to replace the long-familiar dropper bottles of liquid inhalants or "nose drops" for administering the potent bronchodilators and those antibiotics of use in the local treatment of respiratory tract infections

SELECTED REFERENCES

Blythe R H, Grass, G M, and MacDonnell, D R The Formulation and Evaluation of [illegible] 131 206, 1959

Chapman [illegible] ysiological Availability of Drugs

Dragstedt [illegible] Prolonged Action, J A M A 168 1652, 1958

Gruber, Charles M, Jr, Ridolfo Anthony S, and Griffith, Richard S An Enteric Compression Coating III In Vivo Studies With Ilotycin Tablets, J Am Pharm A Scient Ed 47 867, 1958

Jarowski, Charles I Superior Medicinals Achieved by Simple Chemical Modification Tr New York Acad Sc (Series II) 21 290, 1959

Lazarus, J, and Cooper, J Oral Prolonged Action Medicaments Their Pharmaceutical Control and Therapeutic Aspects, J Pharm & Pharmacol 11 257, 1959

THE CHOICE OF DRUGS FOR CHILDREN

Alan K. Done, M.D

INTRODUCTION

The effect of any drug is dependent upon an *interaction* between the drug and the recipient Since individuals may differ markedly in biochemical make up, it is not surprising that there is striking variability in the response to drugs, even among adults When the factor of immaturity is introduced, physiologic and bio chemical differences are accentuated to the extent that the response to drugs can be predicted from adult experience only with considerable reservation Indeed, the realization that children are not simply miniature adults with respect to reaction to disease or response to drugs is a sine qua non of successful pediatric practice

FACTORS IN DRUG SELECTION IN CHILDREN

A number of special problems enter into the proper selection of drugs for children Among these are (1) the effects of immaturity on therapeutic response and toxicity, (2) difficulties in evaluating the effects of drugs, (3) the possibility of affecting growth adversely, and (4) difficulties in administration Immaturity poses additional problems in that it may alter appreciably the response to disease and this, in turn, may influence the indications for, or response to, drug therapy In general, the younger the child the more influential the factors listed above

Once a drug has been selected, there is the problem of deciding upon dosage and the route and frequency of administration The small size of the child is a major, though not the only, problem here Some of the factors which apply to selection of the drug apply as well to the establishment of a safe and adequate dosage schedule

Immaturity and the Response to Drugs—That the infant, especially during the neonatal period differs from the mature individual with regard to functions of organs and tissues is becoming increasingly apparent Recent and current investigations are uncovering more and more examples of incompletely developed enzyme systems, inadequacies in organ functions, and qualitative, as well as quantitative, differences in metabolic pathways in the infant as compared with the older child or adult Some of these factors have obvious implications in terms of the treatment of children, while the therapeutic significance of others is, as yet, obscure Un

fortunately, studies which are performed preparatory to the release of a drug fo marketing seldom include observations on very young animals. However well th action and toxicity of a drug may have been delineated in the mature anima there is no assurance that a similar reaction will occur in the immature organism.

Immaturity may influence the response to treatment either directly throug altered sensitivity to a drug or indirectly through a deficient ability to detoxif and/or excrete the medication. Because little specific information is available, is possible at this time only to enumerate instances wherein immaturity has bee observed to be associated with an altered response or there are strong theoretic reasons for supposing that such an altered response might occur. There is n question that additional study and observation will reveal the problem to exten far beyond these isolated examples, particularly with the development of new, mor potent drugs. The possibility that immaturity may influence response should b considered in the selection of medications for children. Lack of specific knowledg on this point is a distinct contraindication to the use of any drug, at least in th newborn or premature infant and perhaps in older infants as well. As Kretchme so aptly stated, "It is imperative that the pharmacology of an agent be investi gated in the laboratory with the use of fetal and neonatal animals and only whe this specific information is gathered should it be administered to infants."*

ALTERED SENSITIVITY.—Infants and young children are more susceptibl than older individuals to the development of particular types of *toxicity* Generally speaking, they are more prone to develop dangerous disturbances in *acid base equilibrium* in response to drugs with this potential effect. For example, over dosage with salicylates not uncommonly leads to the development of metaboli acidosis in younger children, a complication which is rarely seen in adults eve with comparable blood levels of salicylate.† Serious depletion of sodium and/o potassium from the use of diuretics is more likely to occur in younger children tha in older individuals.

Children seem to be particularly susceptible to *stimulation of the central nervou system* by drugs. Delirium and/or convulsions occur rather commonly in childre in response to toxic doses of drugs which rarely produce these manifestations in adults (e.g., salicylates, antihistaminics, amphetamine and related compounds aminophylline and atropine). The feeling of many that children are more sensitive than adults to *central nervous system depressants* is not well substantiated, although under certain circumstances the effects of drug induced depression are more likely to be deleterious. Dangers inherent in the production of respiratory depression in the face of acid base disturbances are discussed under "Influence of Disease."

LIMITED ABILITY TO DETOXIFY AND/OR ELIMINATE.—There is considerable *evidence that kidney function is not fully developed during early infancy.*‡ Con

*Kretchmer's commentary on the therapeutic implications of immaturity is recom mended reading for anyone concerned with the drug treatment of children.

[illegible] on to ill is

‡Barnett and Vesterdal, in an excellent review, discuss the app [illegible] concerning renal function in infancy to some of the clinical conditions where the *knowledge* [illegible]

sequently, administration to the newborn or very young infant of a drug which depends upon the kidneys for elimination may result in higher blood levels which persist for a longer period of time For example, because of decreased excretion penicillin can be given to infants in smaller doses at less frequent intervals to achieve comparable blood and tissue levels

Recent experiments by Jondorf and associates and by Brown and Zuelzer have indicated that newborn animals may be deficient in the ability to form glucuronides with various compounds Glucuronide conjugation is a major process in the inactivation of a number of well known drugs such as barbiturates, various phenolic compounds, *antipyrine sulfisoxazole* (Gantrisin) *and chloramphenicol* (*Chloromycetin*) It is to be expected that the administration to newborn infants of these and other compounds which depend upon glucuronide conjugation for detoxification may result in a more intense and prolonged therapeutic effect It may also result in the accumulation of toxic levels of the drug or of other materials which must compete with the drug for glucuronide conjugation Deaths have occurred *in premature infants coincident with the administration of large doses of chlo* ramphenicol (Chloromycetin) Presumably inadequate glucuronide conjugation and/or urinary excretion of the drug were responsible for its accumulation in the blood of these infants (Doses of chloramphenicol 25 and 50 mg per kilogram per day in premature and full term infants respectively are said to be safe and are far below those received by the infants who died) Sulfisoxazole (Gantrisin) interferes with glucuronide conjugation and protein binding of bilirubin and its use has been associated with the development of jaundice and kernicterus in premature infants

Evaluation of Drug Effects—Considerable difficulty may be encountered in determining when a child has received an optimal dose of a drug or in detecting the early development of toxicity The infant or young child may be unable to report, or to describe accurately, subjective changes In addition, some of the commonly used objective 'end points' (e g pulse and respiratory rates, blood pressure, activity, clarity of mentation) tend to be less predictable, and therefore less reliable, or may be obscured in the disturbed uncooperative child From a practical standpoint, difficulty in assessing the adequacy of response or the development of toxicity in the child is tantamount to a lowering of the therapeutic index (ratio of toxic to therapeutic dose) of a variety of drugs The possibility that this may be a problem in the individual case should be taken into account in selecting a drug and in following the course of therapy

The use of digitalis serves as an excellent illustration of this point ... signs of digitalis intoxication (anorexia nausea, and cerebral disturbances) are not easily recognizable in infants Consequently, intoxication may not be ... until severe For this reason, when it becomes necessary either to ... digitalis dosage or to 'push' digitalization in the infant, a more rapid ... preparation such as digoxin offers some advantage since it is obvious that any toxicity encountered be of short duration

Influences on Growth—This is of course a problem in drug ... does not exist in the adult The possibility of affecting growth ad... to be an important consideration in the child only with respect to ... ment with hormonal drugs The long term administration of cortis...

compounds may result in inhibition of growth and osseous development The sex hormones, particularly those which are androgenic (e g, testosterone), although capable of stimulating growth, may result in an actual reduction of *ultimate* (mature) height Adult stature is dependent not only on the rate of growth, but also on the age at which growth stops due to closure of epiphyses Since androgens accelerate epiphyseal closure, the advantage of achieving an immediate growth spurt may be overshadowed by an eventual stunting of growth Whether newer anabolic agents with diminished androgenic potency will promote growth but not early closure of epiphyses is doubtful If, in spite of the above, continued androgen therapy for a child is decided upon, periodic x ray examinations should be obtained to permit early detection of a disproportionate advance in skeletal maturation * If this occurs therapy either should be discontinued or reduced, unless the indications for treatment are impellent

Administration of Drugs —Difficulties in administration may, by limiting the available routes by which a drug can be given, influence the choice of medications for a child Vomiting occurs commonly in children as a nonspecific response to illness and may preclude the use of the oral route of administration With few exceptions, however, the oral route is preferable from the standpoint of safety, avoidance of psychic trauma, and the preservation of rapport for future visits The giving of pills to a struggling child or one too young to swallow them may result in aspiration Similarly, the oral administration of oily or irritant medications may, under these circumstances, result in aspiration and the development of a chemical or lipoid pneumonitis

Drugs for oral administration should be made as palatable as possible Distasteful powdered medications may be mixed with jam, jelly, honey, applesauce, or sugar, liquids can be masked with flavored syrups Pleasantly flavored medications for pediatric use are being marketed with increasing frequency However, their palatability increases the likelihood that they will be ingested accidentally in toxic amounts It is safer to render potentially toxic drugs palatable at the time of administration than to tempt children by storing flavored preparations in the home

Where oral medication is not feasible, some drugs can be administered by rectum However, it must be determined beforehand that the substance in question is absorbable by this route This route should not be used in the presence of diarrhea The medication can be suspended in 1 or 2 ounces of water or starch solution and introduced through a catheter or with a bulb syringe The buttocks then should be held or taped together to prevent evacuation In general, the rectal dose is approximately twice the oral dose, though the assumption that this holds for all drugs is neither justified nor safe

Parenteral administration of drugs may be necessary in some instances, but the advantages should be weighed against the psychic (and physical) trauma entailed by injections

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* [illegible] found that a dose of 5 mg of testosterone per day was as effective [illegible]

INFLUENCE OF DISEASE

Certain characteristics of the childhood response to disease should be considered in selecting drugs for infants and children

Narrow Margin for Error—There is a *greater tendency for the dissemination or rapid progression of infection in children* That is to say, there is a lesser margin for error in selecting the correct antibacterial drug and dosage schedule initially Inappropriate or inadequate treatment with an antibiotic or chemotherapeutic agent may, through the loss of valuable time permit progression of the infection and the development of dangerous complications Errors of this type are usually related to a failure to establish the correct etiologic diagnosis

It is neither practical nor rational however to delay antibacterial therapy pending availability of bacteriologic data in the child in whom such treatment seems definitely indicated A satisfactory alternative is to cover" the likely diagnostic possibilities with appropriate smears and/or cultures (nasopharyngeal, blood, spinal fluid, stool etc, as indicated in the particular case) prior to institution of treatment The agent then selected should provide therapeutic coverage for the likely etiologic possibilities This is particularly important in circumstances where it is not possible to obtain bacteriologic studies At times, it is wise to institute treatment on the basis of epidemiological information For example, if a child has meningococcemia and a sibling is found to be ill it is only sensible that treatment should not be denied the latter until the culture is reported or the clinical picture has become definable (and perhaps, irreversible) If and when cultures indicate that an inappropriate antibiotic was selected and/or it becomes obvious that the clinical course is not being affected favorably therapy should be changed accordingly

Adequate coverage of etiologic possibilities and the prompt institution of *indicated* changes in the therapeutic program are particularly critical in such serious childhood infections as meningitis osteomyelitis pyelonephritis, septicemia, and in *any* infection in the newborn infant

Disturbances in Internal Homeostasis—In the infant and young child, *fluid balance and acid-base equilibrium are disturbed more easily* and by a wider variety of abnormal circumstances than in the adult Vomiting diarrhea, fever, excessive sweating, and hyperpnea, each of which may result in the loss of substantial amounts of fluid, are seen as specific or nonspecific manifestations of illness far more commonly and to a greater degree in children than in adults This problem is complicated further by the fact that maintenance of an adequate fluid intake is often difficult in the child who is ill and anorectic Thus, dehydration, albeit subtle at times, is a relatively frequent occurrence in sick children and may result in significantly reduced renal function, particularly in infants

Under these circumstances, the administration of a potentially toxic drug which is eliminated by the kidneys may be followed by hazardous accumulation Furthermore, the potential deleterious effects of a drug on acid base equilibrium may be enhanced For example, the administration of salicylate in usual therapeutic doses to a dehydrated infant or young child may lead to dangerous intoxication higher blood levels of salicylate may occur and, with or without this factor, acidosis is more likely to develop

The production of respiratory depression by drugs may aggravate disturbances in acid-base equilibrium in the child. Not only is respiratory compensation eliminated, but respiratory acidosis may be superimposed. For this reason, potentially depressant drugs, such as paregoric, should be used with extreme caution in the infant with severe diarrhea. Similarly, opiates should be used with caution in infants subjected to prolonged fluid deprivation incident to surgery.

DOSAGE CONSIDERATIONS

There are few drugs for which adequate data are available concerning optimal doses for children. Consequently, various formulas, usually based on age or weight have been devised for calculating pediatric doses from those known to be effective in adults. However, these rules are not applicable to patients of all sizes. For example, the usually recommended digitalizing dose of digitoxin ranges from 0.02 to 0.06 mg. per kilogram; within this range, the younger the child, the higher the dose per kilogram of body weight. In small children, sulfadiazine is used commonly in doses of 200 mg. per kilogram in the treatment of severe infections; in a 70 Kg. adult, this would amount, on the basis of body weight, to a dose of 14 Gm.

Table 1. Determination of Children's Doses From Adult Doses on the Basis of Body Surface Area

Weight Kg	Weight Lb	Surface Area (Sq. Meters)	Fraction of Adult Dose*
2	4.4	0.15	0.09
4	8.8	0.25	0.14
6	13.2	0.33	0.19
8	17.6	0.40	0.23
10	22.0	0.46	0.27
15	33.0	0.63	0.36
20	44.0	0.83	0.48
25	55.0	0.95	0.55
30	66.0	1.08	0.62
35	77.0	1.20	0.69
40	88.0	1.30	0.75
45	99.0	1.40	0.81
50	110.0	1.51	0.87
55	121.0	1.58	0.91

*Based on average adult surface area of 1.73 sq. M.

Crawford and associates, Snively, and others have noted that many of the fundamental physiologic processes such as water, electrolyte and caloric requirements, plasma volume, oxygen consumption, and glomerular filtration are essentially constant when compared on the basis of body surface area. The studies of Crawford and co-workers suggest that the calculation of dosage in terms of surface area offers the advantages of greater simplicity and accuracy than calculations based on body weight or age. Although there is some doubt as to the validity of body surface area as a unit of physiologic function, its application to the calculation of drug doses, other factors being equal, eliminates the need for using different dosage standards in various age groups.* For example the average digitalizing dose of

*Snively presents an illuminating discussion of the use of body surface area as a dosage criterion for fluid therapy from the standpoints of theory and clinical application. Oliver and associates have challenged the acceptance of surface area as a unit of physiologic function.

digitoxin is 0 75 mg per square meter of body surface area, regardless of the age or size of the individual However, the observations cited in the section "Immaturity and the Response to Drugs" suggest that neither weight nor body surface area is a sufficient criterion for the accurate administration of drugs to infants In the latter, it is imperative that the physician know whether immaturity poses problems other than the small size of the individual before *any* dosage criterion is employed When available, experimentally determined or clinically established doses are to be preferred to those calculated on the basis of adult dose, regardless of the method of calculation

Table 1 presents figures for estimating childhood doses of drugs from adult doses on the basis of body surface area

It should be emphasized that no method of calculating doses provides for individual variations in response or obviates the necessity for careful clinical appraisal of appropriateness of dosage

SELECTED REFERENCES

Barnett H L, and Vesterdal, J The Physiologic and Clinical Significance of Immaturity of Kidney Function [illegible]

Brown, A K and Zuelzer, W [illegible] Conjugating System [illegible]

Crawford, J D, Terry M [illegible] tion by Aplication [illegible]

Goodman, L S, and Gilma [illegible] York 1955 The Macmillan Co

Jondorf, W R, Maickel, R P and Brodie, B B Inability of Newborn Mice and Guinea Pigs to Metabolize Drugs, Biochem Pharmacol 1 352, 1959

Kre [illegible] -mical [illegible]

Kre [illegible] 1959

Lei [illegible] 157, 1955

Nadas, A S Rudolph, A M, and Reinhold, J D L The Use of Digitalis in Infants and Children New England J Med 248 98 1953

Nelson, W E Textbook of Pediatrics, ed 6 Philadelphia, 1954, W B Saunders Co

Neter, E, and Karzon, D T Pediatric Dosages and Routes of Administration of Antibiotics, [illegible] May, 1956

[illegible] Lack of Scientific Validity of Body Surface [illegible] A M A 167 1211, 1958

[illegible] Digoxin Dosage in Infants, Pediatrics 18 730, [illegible]

Snively, [illegible] Theory and [illegible]

Sobel, E [illegible] e of Methyl [illegible] aturation and Linear Growth, J Clin Endocrinol 16 241, 1956

Unna, K R, Glaser, K, Lipton, E, and Patterson, P R Dosage of Drugs in Infants and Children I Atropine, Pediatrics 6 197, 1950

Wallace, W M The Use of Salicylates in Pediatrics, Quart Rev Pediat 9 135, 1954

THE CHOICE OF AGENTS TO ADJUST AND MAINTAIN INTERNAL HOMEOSTASIS

Paul L McLain, M D , and
Frederick R Franke, M.D , D Sc (Med)

INTRODUCTION

The concept of internal homeostasis, first clearly enunciated by Claude nard, is now thoroughly entrenched in medical thinking Indeed, the preserv of a cellular environment consistent with normal function may well be consic the ultimate purpose of most physiologic mechanisms, and the restoration or n tenance of such conditions the ultimate aim of most if not all therapy So b a view, however valid is rather esoteric, but there is an area of practical th peutics which bears directly on the problem, namely, that pertaining to the n tenance and repair of the various body fluids The present chapter is restr largely to this latter field

The following brief review of fluid distribution and composition in the hu body is presented as a background for discussion of specific therapeutic meas

The Fluid Compartments—Many valid considerations support the con that body fluids occupy three major compartments, separated from each othe cellular membranes which are, in general, freely permeable to water and to n organic and inorganic solutes nearly impermeable to particles of the dimens of proteins and somewhat selectively permeable to certain critical ions suc Na^{+}, K^{+}, Mg^{+} , and Cl The three compartments are designated respectively cellular, comprising the fluid of the cells themselves, interstitial, consisting of fluid immediately surrounding the cells, and vascular, comprising the fluid of blood plasma The term extracellular fluid is often employed and includes b interstitial and vascular fluids It is important to realize that all fluid exchar between the organism and its environment must be mediated through the vasc compartment the avenues for such exchange being the skin, the lungs, the gut, the kidneys Similarly, the only avenue of exchange between the cellular and vascular compartments is the interstitial fluid Thus, the integrity of the cell fluid is guarded from environmental onslaught by two "buffer states"

Volume of Body Fluid—The volumes of fluid in the several compartments ted … derable … portant … b t the methods available yield clinic

useful results. One of the chief determinants is body size, especially the lean body mass, and there is apparently a notable difference between the sexes. A frequently quoted working estimate for a 70 Kg. man places the volume of the vascular compartment (expressed as plasma water) at 3 liters, that of the interstitial compartment at 14 liters, and that of the cellular compartment at 29 liters. According to this estimate, the total body water is about 660 ml. per kilogram of body weight. One must not confuse the vascular fluid compartment with the total blood volume, since the latter includes about 45 per cent of cellular material whose fluid correctly belongs to the cellular compartment.

Composition of Body Fluids.—The body fluids are essentially solutions of electrolytes in which the opposing ionic charges are balanced. Each fluid compartment of the body has a distinctive solute pattern, which is apparently determined by the relative diffusibility of the various materials through the several separating membranes. It is generally held that the final distribution of ions at equilibrium on the two sides of a membrane is in accord with the Donnan theorem, which states, in effect, that the concentration products of the diffusible anions and cations on opposite sides of the membrane are equal. The presence of large numbers of poorly diffusible ions, such as the protein anions in plasma and cellular fluid, results in differences among the compartments in their total electrolyte concentrations. Thus, the total electrolyte concentration of plasma is about 310 mEq. per liter, that of interstitial fluid about 300, and that of cellular fluid about 390 (Table 2). In general, the greater the concentration of nondiffusible ions, the greater is the total electrolyte concentration.

*Table 2. Normal Electrolyte Patterns of the Body Fluids**

	Plasma (mEq./Liter)	Interstitial Fluid (mEq./Liter)	Intracellular Fluid (mEq./Liter)
Cations			
Na^+	142	138	14 (?)
K	5	5	157
Ca^{++}	5	5	–
Mg^{++}	3	3	26
Totals	155	151	197
Anions			
Cl	103	108	?
HCO_3	27	27	10
HPO_4	2	2	110
SO_4	1	1	1
Organic Acids	6	6	–
Protein	16	2	74
Totals	155	146	195

Note. Apparent imbalance of total anions and cations results from uncertainty of some of the analyses.

*After Bland, J. H.: The Clinical Use of Fluid and Electrolyte, W. B. Saunders Co., 1952.

Excepting its relatively great protein content, plasma has virtually the same chemical composition as does interstitial fluid. This fact is of great practical importance because it permits inferences concerning the composition of interstitial fluid from chemical analysis of plasma, a much more accessible fluid. In both, the

major cation is Na^+, and the major anions are Cl^- and HCO_3^- Both fluids contain *small concentrations of* K^+, Ca^{++}, Mg^{++}, HPO_4^{--}, SO_4^{--}, and anionic organic material Both contain small concentrations of nonelectrolytes, the most impressive of which, quantitatively, are phospholipids, cholesterol, neutral fat, and glucose

Cellular fluid differs markedly from extracellular Here, the chief cation is K^+, while only small amounts of Na^+ are ordinarily found, and Mg^{++} is much more prominent than in plasma or interstitial fluid Among the anions, Cl^- is conspicuous by its scarcity, its place being taken largely by HPO_4^- The concentration of HCO_3^- is lower than in extracellular fluid, that of SO_4^{--} about the same The protein concentration of cells is, of course, greater than that of plasma, and far exceeds that of interstitial fluid

Dynamics of Body Fluids —Again with the exception of protein differences the striking feature of comparison *among the various fluids is the tendency of* Na^+ and Cl^- to remain extracellular while K^+ and Mg^{++} become concentrated within the cells The cause and full significance of this distribution are not understood, but for all practical purposes one may consider that the capillary membrane is *freely permeable to these ions while the cell has* some mechanism, whether or not it be a property of the membrane, which normally keeps it nearly free of Na^+ and Cl^- The property just described, often called selective permeability, is impaired when cells are damaged or killed Under these conditions the segregation of Na^+ and K^+ into separate compartments disappears

DIFFUSION —While the fluid compartments are anatomically distinct, physiologically they form a sort of continuum subject to massive exchanges of materials, especially water Several kinds of forces are active in producing shifts of water, ions, and nonelectrolytes among the fluid spaces Perhaps the most important of these is *diffusion* the migration of a particle species in response to a concentration gradient Diffusion across membranes can occur, of course, only if the membrane is permeable to the ions or molecules in question In general, a material which is diffusible (i e to which the membrane is permeable) will tend to move in the direction of the lower concentration of that particular material until the concentrations on each side of the membrane are equal At this point, rates of diffusion are equal in the two directions, and migration apparently ceases In the case of the body fluids, as noted above, the equilibrium state is not that of equal concentrations of all diffusible ions because of the restraining effects of the undiffusible ions such as proteins

OSMOSIS —*Materials* in solution, even when they are rather freely diffusible, are responsible for movement of water across membranes by the process called *osmosis* Strictly, osmosis is diffusion of water rather than of solute It depends upon the fact that, in relation to the body membranes body water is much more *diffusible than any of the materials normally* dissolved in it If, therefore, unequal total concentrations of solutes exist on opposite sides of a membrane, the same must be true of water Water then diffuses in the direction of the greater solute concentration because that is the direction of the lower water concentration In the *case of diffusible solutes, the* water diffusion has the greater velocity, and there will be some exchange of solute in the opposite direction before equilibrium is attained Nondiffusible solutes, on the other hand, are trapped on one side of the

membrane, and water transfer is the only means of approaching equilibrium. In general, the osmotic activity of dissolved material depends upon the total particle concentration of the solute or solutes present. In this regard, ions are the equivalent of molecules. When the system is in equilibrium the *osmotic* activities of the three fluid compartments of the body are nearly equal, i.e., the vascular, interstitial and cellular fluids are isotonic, each with the others.

HYDROSTATIC PRESSURE.—Since diffusion across membranes depends upon the random contact of particles with the membrane, forces which increase the likelihood of such contact will increase the rate of diffusion. *Hydrostatic pressure* is such a force and it operates especially between the vascular and interstitial fluid compartments. The blood pressure in the capillaries has an important influence on the diffusion of vascular fluid into the interstitial space. This effect is not balanced by any comparable hydrostatic pressure in the tissues, but the osmotic effect of the plasma colloids, tending to effect diffusion of water from the interstitial into the vascular compartment, is of comparable magnitude and, in fact, often exceeds the blood or plasma hydrostatic pressure. The balance of these opposing forces determines the direction of fluid exchange at any point in the vascular tree where such exchange is possible.

The mechanisms of fluid and solute exchange thus far considered are purely physical. There are situations, however, in which material is transferred from one compartment to another against a concentration gradient. Such is the case, for example, in the exclusion of Na^+ and Cl^- from cells and in the intracellular accumulation of K^+ and Mg^{++}. Maintenance of concentrations in opposition to physical gradients is assumed to require metabolic work which in the cases mentioned, is performed by the cells. The details of this cellular operation can only be surmised at present and are not essential to practical application of the result.

BUFFER SYSTEMS.—Another important property of the body fluids, intimately related to their chemical constitution, is reaction or hydrogen ion concentration. Through a series of so called buffer systems, the extracellular fluids are normally maintained in a slightly alkaline state not far from neutrality (pH 7.36-7.41). The chief characteristic of a buffer system is its ability to withstand the addition of relatively large amounts of acid or alkali with only a small shift in final reaction or pH. This effect depends upon the ionization characteristics of weak acids and their salts, whereby both the undissociated molecule and the anion exist simultaneously in the fluid. A typical body buffer system comprises $NaHCO_3$ and H_2CO_3. The $NaHCO_3$ provides the ion HCO_3^-, which, with the undissociated acid, makes up the requisite combination. Addition of a strong acid to a solution containing these two substances has the effect of increasing the concentration of nonionized H_2CO_3 at the expense of the HCO_3. The actual change of pH is much smaller than that which would occur in the absence of the buffer system.

In addition to the bicarbonate system, body fluids are buffered by phosphate and protein systems which operate in a similar manner. Proteins are highly important buffer constituents of blood and cells. Two or more sets of buffers interact in such a manner that the final pH corresponds to the final concentration ratio of any of the buffer pairs. It is possible, therefore, to estimate pH from analyses for a single buffer pair, such as HCO_3 and H_2CO_3. The relationship is expressed

the following form of the familiar Henderson Hasselbach equation

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

There is ample evidence that the volume, composition, and reaction of the body fluids are important to the organism. They are normally maintained within remarkably narrow limits, and serious dislocations are attended by some danger. Abnormalities in volume may be estimated by dilution methods, but are, in practice, often inferred from clinical data and from the results of physical and chemical analysis of the blood and plasma. Reaction may be measured, calculated, or simply inferred. Rational therapy directed toward the body fluids must, of course, take cognizance of the abnormalities known or assumed to exist, and is based upon the principles here considered.

CLINICAL APPLICATIONS

Internal homeostasis is dependent upon adequate intake of electrolytes and water (which are usually consumed in excess of actual needs), balanced by selective excretion. Water loss is partitioned, in the main, between skin and lungs on the one hand and the kidneys on the other. Under ordinary conditions, extrarenal excretion of water occurs without important loss of electrolytes. It is an important factor in the regulation of body temperature and is markedly altered by environmental conditions and by disease. Urine volume varies so as to complement extrarenal water loss in balancing the intake. The kidneys also assume the major role in electrolyte excretion and conservation. Urinary output is regulated by a complex system of receptors and effectors which include the hypothalamus and posterior pituitary.

Disturbances in Homeostasis

Abnormalities of the body fluids may be classified, for the sake of convenience, into two broad categories: those of volume or distribution, the effects of which are predominantly mechanical, and those of composition, with chiefly chemical or metabolic consequences. The distinction is somewhat artificial, since volume and composition are not independent variables. However, there is justification for considering one or the other factor as dominant in many clinical situations.

Disturbances in Volume.—Abnormalities in volume may, of course, be in either direction and tend to distribute themselves, albeit unevenly, among all the fluid compartments. The cellular compartment is remarkably well protected against large variations in volume and is, in any case, relatively inaccessible to examination. The extracellular volume is much more labile and not infrequently undergoes significant changes, with readily recognizable results.

Decrease in Extracellular Fluid Volume.—Independent alterations of vascular and interstitial volumes do not long persist because the capillary membrane is freely permeable to water and most solutes, and large gradients may be developed rapidly. It is possible, however, to have in effect an almost pure or uncomplicated depletion of the vascular compartment for a long enough period to produce serious trouble. The most obvious example of this condition occurs with sud

den and severe hemorrhage. If the vascular volume is decreased beyond the ability of the organism to compensate by vasoconstriction, venous return to the heart is impaired and cardiac output falls. The critical result of this sequence is diminution of oxygen delivery to the tissues. It should be emphasized that these events may occur without anemia and, indeed, with a normal amount of circulating hemoglobin. The defect is primarily one of circulating volume; it may be aggravated, of course, by co-existing hemoglobin deficiency. If defective oxygenation of the tissues is allowed to persist, irreversible changes occur which make restoration of function difficult or impossible.

Causes. In general, significant reduction in vascular fluid volume is apt to be a part of the clinical syndrome usually referred to as "shock." In such conditions, the plasma volume may be reduced with little change in the actual red cell volume. Extensive burns, crushing trauma, and intestinal obstruction are offenders in this respect. Of course, the dynamic effects of low blood or plasma volume are evident whether or not there are co-existing abnormalities in the other fluid compartments.

When plasma volume is reduced, some depletion of interstitial volume almost certainly occurs within a short time. Consequently, from the standpoint of fluid balance, the extracellular compartments are properly considered together. The clinical states mentioned above actually reduce the volume of the entire extracellular space. Moreover, the changes may not be properly distributed to bring into prominence the mechanical effects upon the circulation which are so characteristic of severe blood or plasma loss. Thus dehydration, as from excessive sweating, water deprivation, diuresis, or diarrhea, may seriously deplete the extracellular, or even the intracellular, fluid without inducing circulatory collapse.

Shocklike states, associated with hypotension, favor transfer of fluids from the interstitial into the vascular compartment. Extensive vasodilation may produce a relative hypovolemia, with the general dynamic phenomena of reduced blood volume, but without actual loss of fluid from the vascular circuit. Under such conditions (e.g., in so-called neurogenic shock), decrease in interstitial volume may occur while plasma volume actually increases.

Water loss, both renal and extrarenal, derives immediately from the extracellular fluid compartment. In order to maintain internal homeostasis water loss to the environment is followed immediately by adjustments in the other compartments to protect the body against marked changes in a single compartment. Thus, loss from the extracellular fluid is compensated by release of water from the cells because of the resultant increased osmolarity of the extracellular fluid; loss of potassium from cells causes even greater cellular dehydration.

Dehydration is one of the most common and important causes of volume defect and, depending upon its rapidity of development, may be considered either acute or chronic. Clinically it is seen in subjects whose water intake is markedly decreased. This status may be self-imposed as in the psychotic or aged, associated with infection, brain injury, pain, drugs, and sedatives, or related to physician dictum as frequently seen in pre- and postoperative fluid restriction. As the body solutes become more concentrated, subjective and objective manifestations occur. Thirst is a frequent complaint, increasing as urine volume decreases and its specific

gravity rises Mental changes such as lassitude and apathy develop going on to disorientation confusion and even mania Signs of dryness are seen in the condition of the tongue and mucous membranes poor tissue turgor and soft muscles and eyeballs *Decreased blood pressure rapid pulse and even peripheral circulatory failure may develop*

Increase in Extracellular Fluid Volume —Plethora occurs as an isolated phenomenon chiefly in response to overenthusiastic fluid therapy Excessive intake of water or hypotonic solutions of crystalloids will produce a primary increase in plasma volume which is soon shared by the interstitial spaces Hypertonic solutions or more particularly colloid solut ons (including plasma and blood) can on the other hand induce sufficiently high blood volumes to embarrass the circulation with little immediate effect on the interstitial compartment

Excessive oral water intake with properly functioning renal and adaptive mechanisms will not produce positive water balance and retention The kidneys rapidly excrete the water so that loss equals intake and with overwhelming intake excretion may be so massive as to result in a decrease in body weight

More commonly excess of extracellular flu d is the result of some circulatory or renal deficiency which interferes with proper elimination of water In disease states associated with oliguria or anuria water overloading which cannot be met by increased excretion through insensible routes results in increased total body water both extra and intracell ılar The effect is then that of sodium and potassium dilution with water intoxication Subjective and objective signs of excessive hydration are related to the increased volume of water and also to its excess in relation to sodium content The manifestations may be associated either with increased intracranial pressure dilution of electrolytes or excretion of water excess The first two conditions prodı ce headache papilledema vomiting muscular cramps or twitchings respiratory changes and convulsions while water excess is partly relieved by vomiting diarrhea and excessive salivation Hypertensive encephalopathy and the central changes of eclampsia may be due to water intoxication Vascular engorgement results in pressure elevation skin edema and the excretion of low gravity low chloride urine Blood analyses may show dilution of solutes and cellular elements

Disturbances in Composition —

Relation Between Volume and Composition —In the maintenance of the internal environment of the body water content and sodium concentration are interdependent although a deficit of one without a corresponding deficit of the other may well occur The demand of a known amount of sodium for a certain amount of water is well established Changes in electrolyte pattern and concentrations of specific ions may be more important in their effect on body well being than even changes in water volume Examples of this occur in such states as severe hyponatremia or acidosis Certa nly changes in volume and extracellular flu d composition are met with changes in intracellular volume and composition Present concepts relating to sodium retention as the background for the development of congestive failure indicate the complexity of the interrelationship between volume and composition The problem of acid base balance further complicates the fluid

position, concentration, and regional distribution are present simultaneously, and therapy may have to be aimed at the one which seems clinically the most important

ALTERATION IN ELECTROLYTE PATTERN —Paleochemistry would seem to indicate the evolutionary relationship of our extracellular fluid with marine ancestry Particularly suggestive is the similarity of sodium concentration in extracellular fluid and sea water, although total ionic concentrations are different The fluid compartments of the body have been reconstructed experimentally from data on the intact organism by dilution techniques isotope dilution and turnover techniques, balance studies, and analysis of tissue samples Such information now enables us to estimate the composition of body fluids in both health and disease Bicolumnar diagrammatic representation of cations and anions making up the total ionic composition of the extra- and intracellular fluid is common practice and is used clinically as an aid in diagnosis and therapy Clinical inferences as to specific ion content may be made from analysis of extracellular sodium, potassium, chlorides, and bicarbonate, and therapy is guided by serial determinations to estimate intracellular change

Specific Important Ions While sodium is the predominant extracellular cation, chloride is the main anion and, although their concentrations are not identical, they are associated in a proportion of 3 2 Since chloride determinations are more available and perhaps generally more accurate than those of sodium, chloride analysis may serve as a guide to changes in both ions In disease states, the proportion may be disturbed, so there are limitations to the evaluation of body fluids and required therapy by this method

Sodium is maintained at a constant level despite alterations in intake chiefly by tubular reabsorption of the filtered ion Adrenal corticosteroids, possibly a specific one, aldosterone, control this function in association with the anterior pituitary and higher brain centers

Ingested potassium, which is perhaps more incompletely absorbed than sodium, enters the intracellular fluid, where its concentration is some 15 to 20 times the extracellular, or it may be excreted by way of the skin, intestinal tract, or urine Since growth, repair, and glycogenesis require potassium, its intracellular importance is obvious Regulatory mechanisms keep the low extracellular potassium levels relatively constant, but intracellular potassium may be decreased considerably The adrenal corticosteroids which facilitate tubular reabsorption of sodium increase tubular secretion or markedly limit tubular reabsorption of potassium

In general, chloride is maintained by the same factors which regulate sodium In disease or stress, the effect of adrenal cortical hormones is probably more upon sodium than upon chloride Vitamin D and the parathyroid hormone regulate calcium and phosphorus metabolism either by increasing absorption of ingested calcium or by increasing excretion of inorganic phosphorus from the body Regulation of magnesium is poorly understood at present but elevations are associated with renal failure and diabetic coma, while depletion is associated with vasomotor depression, respiratory failure, and hypothyroidism

Alterations in Acid-Base Balance Since metabolism produces sufficient acid to alter seriously the buffer system guarding body pH, this system must maintain its integrity for the protection of the internal environment Studies on the status of any buffer system such as, for example, that of bicarbonate are valid for that

system in intracellular as well as extracellular compartments To maintain the constancy of pH with continuously acid producing metabolism, elimination of relatively strong acids neutralized by the buffer system must take place This is accomplished by excretion of free organic acids in acid urine as well as monobasic phosphates as buffer pairs The latter are in salt to acid ratios which are smaller than those of the ultrafiltrate from which the urine was formed, so that base is conserved Ammonium salts of these acids and ammonium ion formed from ammonia remove both the anion and cation (hydrogen ion) of the original acid Alkali cations are further conserved by the tubular excretion of hydrogen ions, which further acidifies urine By such action, which is essentially elimination of stronger acids than those neutralized, the buffer system ratios, and hence the pH, are kept constant Carbonic acid is eliminated by way of the lungs as carbon dioxide, in alkalosis, bicarbonate may be excreted by the urine with the excess cation, and chloride is retained

Bicarbonate makes up approximately one-fifth of the anions, protein one tenth, and chloride the remainder As long as buffer salts are available, carbon dioxide, being constantly produced by metabolism, serves as an inexhaustible source of reserve bicarbonate No such reserve of chloride is available but total anion concentration is adjusted by the ability of the body to convert carbon dioxide to bicarbonate and to excrete carbon dioxide by ventilation or bicarbonate in the urine Sodium makes up approximately nine tenths of the total cation and is roughly proportional to the sum of the bicarbonate and chloride anions except in disease, when the other anions (organic acids, sulfate, phosphate) may be in excess of normal

Clinical States Commonly Associated With Ion Defects Starvation occurs in clinical conditions which interfere with the intake of foodstuffs Loss of weight is associated with loss of body substance, mainly fat stores and tissue protein Nitrogenous wastes as well as acetone bodies tend to accumulate with this process, and potassium is released from cells As potassium enters the extracellular fluid, its excretion is increased but considerable conservation takes place so that sodium excretion is markedly diminished Late effects include increases in extracellular volume, decreased protein levels and lowered cholesterol

Vomiting leads essentially to dehydration and starvation, with the added effect of loss of electrolyte in the vomitus Large quantities of sodium potassium, and chloride are lost in this way, as well as large volumes of body water Metabolic alkalosis occurs, with chloride loss disproportionately greater than sodium loss compensated by retention of carbon dioxide, increase in bicarbonate, and resultant rise in pH

Diarrhea is similar to vomiting except that the loss of electrolytes in liquid stools includes bicarbonate in addition to sodium and potassium Metabolic acidosis therefore occurs and may be increased by starvation, renal failure, and hyperchloremia Dehydration may be so severe that normal or elevated plasma electrolyte concentrations may be observed despite marked body depletion

Sweating as seen in fever states or elevated environmental temperatures incurs losses of sodium, chloride, and potassium beyond the renal excretion of these substances and may produce important deficits

Kidney malfunction may exaggerate volume deficits of any type if the reabsorptive capacity of the tubules is impaired Conservation of sodium and chloride usually persists even in advanced kidney disease so that deficits in these ions do not usually occur Chronic renal disease may occasionally be associated with potassium loss Renal loss of phosphate may occur under unusual conditions as may deficits of calcium and protein

Excesses of sodium and chloride occur frequently in patients with normal excretory apparatus and are seen for example in premenstrual fluid retention Since sodium excretion may be based upon several previous days intake, warm weather weight changes may be associated with relative sodium retention Disease of the kidneys endocrines and central nervous system are associated with salt retention edema and congestive failure Salt retention and edema may also develop during certain stages of hepatic cirrhosis and the toxemias of pregnancy The underlying cause here may be specifically related to excessive tubular reabsorption of sodium (and therefore chloride) because of excessive adrenal cortical or some related function

Excesses of potassium like those of sodium are related to volume changes Hyperkalemia may be a manifestation of dehydration rather than of increase in total potassium Extracellular increase in potassium such as may occur in anoxia diabetic coma and diarrhea is rapidly disposed of by the kidneys so that persistent elevations are seen usually in association with anuria or oliguria An increase in total potassium would occur only in kidney disease or some disturbance of excretion such as adrenal insufficiency Cellular potassium increase at the expense of extracellular potassium may occur in periodic paralysis with insulin or glucose therapy or cell repair Muscular and neurological function may be altered by potassium variation The former is commonly detected in the electrocardiogram Since the electrocardiogram reflects cellular potassium the typical effects of hyperkalemia in the trace may precede or lag those of extracellular potassium by some 24 hours

Acid base disturbances may be of the metabolic type usually associated with a primary disturbance of the bicarbonate buffer system or the respiratory type associated with alteration of carbonic acid elimination In these disturbances protective mechanisms may maintain the pH but associated changes in volume and composition of body fluids frequently occur Much of the symptomatology may therefore be due to loss of body water and sodium as previously discussed Metabolic alkalosis due to alkali retention is not commonly seen but is produced when excess bicarbonate is given Related to it is sodium retention, so that fluid retention and edema may also be present Metabolic alkalosis due to acid loss is frequently seen in prolonged and severe vomiting with loss of hydrochloric acid related to this is dehydration Loss of extracellular fluid may be so marked as to keep electrolyte concentrations deceptively high Metabolic acidosis is observed more frequently than alkalosis and may be due either to retention of acid or to alkali loss In the former carbon dioxide combining power decreases as buffer salts react with stronger acids produced by altered metabolism Excretion of acid depletes sodium and with this decrease in sodium extracellular fluid volume decreases Characteristically electrolyte analysis reveals increase in organic acids reduction of bicarbonate compensatory loss of carbonic acid with hyperventilation and reduction of chloride Metabolic acidosis may be due to alkali loss because of inability of

the kidney to conserve base or from severe loss of lower intestinal tract secretic Here loss of chloride and fluid is accompanied by dehydration Critical acid may be present with relatively little change in carbon dioxide combining po because of fluid loss, but the loss of alkali may be such that only a slight furt progression of acidosis can be overwhelming Respiratory alkalosis may be s in any clinical condition characterized by marked hyperventilation Here re loss of bicarbonate takes place, with resultant decrease in carbon dioxide comb ing power which may be mistaken for acidosis With this type of alkalosis, urine is alkaline and follows the pH of the plasma Respiratory acidosis is se when carbon dioxide accumulates due to pulmonary disease With this type acidosis, the alkali reserve rises to accommodate to the carbon dioxide excess possible false interpretation of alkalosis may be avoided by demonstration of a urine or decreased serum pH

ALTERATIONS IN COLLOID PATTERN —Plasma colloid depletion, by diminishi the colloidal osmotic activity of the plasma may upset the normal balance of for controlling the exchange of fluid between the vascular and interstitial compa ments Specifically, this defect leaves the hydrostatic pressure in the capillar relatively unopposed, and favors transfer of fluid from the plasma into the inte stitial compartment The edema of hypoproteinemia has been generally attribut to such an effect A similar result would follow from excessive leakage of prote from plasma into the interstitial fluid Normally, a small amount of such prote leakage is known to occur, but the colloid is prevented from accumulating in t interstitial fluid by virtue of the lymphatic drainage Should the lymphatics blocked or otherwise rendered nonfunctional, the rising colloidal osmotic activi of the interstitial fluid, especially in view of the low hydrostatic pressures of tl tissues, would favor edema formation at the expense of plasma water

ALTERATIONS IN RESPIRATORY FUNCTION OF THE BLOOD —The importance f homeostasis of adequate oxygenation of the tissues requires no discussion, nor do the relationship of hemoglobin concentration or oxygen carrying power of blood the entire process of cellular respiration The most important defect in this are is anemia, which, of course, has numerous causes The effect of anemia may b produced by intoxicants which, like carbon monoxide or methemoglobin former render the hemoglobin incapable of carrying the normal oxygen load Enzym poisons such as the cyanides, prevent the uptake of oxygen by the tissues even fron normally oxygenated blood

Hemoglobin excess is not of itself harmful, but mechanical difficulties ma result from a severe polycythemia Polycythemia may be associated with increasec normal, or diminished blood volume, and the effects of these are not related to th excess of cells If, however, there is a marked increase of red cell volume relativ to plasma volume, the viscosity of the blood is increased in proportion to this ex cess While it is possible that high viscosity may result in sluggish circulatioı through the capillaries, the viscosity change associated with moderate polycythemi is probably of little importance

GENERAL PHARMACOLOGIC CONSIDERATIONS

In general, the rational treatment of fluid imbalance is directed toward the spe

been implied, the abnormalities are usually multiple, although one may predominate in a given situation The major therapeutic objectives constitute the primary subdivisions of this section Extensive advice of a specific nature is included in the many excellent monographs available and cannot be included here

Fluid Replacement—Replacement therapy is designed to restore the normal physicochemical environment of the cells and the normal volume relationships of the fluid compartments of the body The plan of therapy is based upon some sort of estimate, preferably both qualitative and quantitative, of the existing state of the body fluids Decision as to how much of what kind of fluid to administer requires, in addition to certain laboratory aids, no little clinical knowledge and judgment, since estimates of abnormalities in volume and/or composition are, at best, imprecise It is important, in other words, to know how various clinical entities generally affect the fluid balance In addition, the clinical situation introduces the element of time and dictates whether the treatment must be immediate and heroic or may be expectant and conservative Similar considerations will affect decisions regarding the route of administration

The greatest danger in connection with fluid therapy is overdoing it This possibility exists both for fluid volume and for certain specific constituents Accordingly, experienced clinicians do not attempt a complete correction of estimated deficits within the first 24 hours of treatment, especially when the deficits are thought to be great The implication is not, of course, that large volumes may not be given within a short time when indicated, as, for example, in severe hemorrhage or advanced dehydration but that the first estimate of total requirement may be in serious error, and that certain physiologic mechanisms may be overtaxed The only safe guide in the course of fluid therapy is the response of the patient, assessed by his clinical progress and the results of timely laboratory examination of his blood and urine

It is well to remember that the administration of large quantities of fluid parenterally may result, inadvertently, in giving too much of some particular constituent of the solution Each liter of 0 9 per cent sodium chloride solution, for example, contains 9 Gm of salt, including about 155 mEq of sodium This is a considerable fraction of the average daily sodium turnover Several liters of such a fluid might be administered in the course of 24 hours, and under conditions of impaired sodium excretion Special caution must be exercised in the administration of solutions containing potassium because of its marked toxicity on the heart While less often given in dangerous quantities, the magnesium ion, likewise, is far from innocuous

The hazards of overloading the circulatory apparatus have already been mentioned In general, solutions of crystalloids are better tolerated from this standpoint than are the colloidal "plasma expanders" because the former readily escape from the vascular tree into the interstitial spaces Blood and plasma infusion have their special dangers such as incompatibility, nonspecific febrile reactions, and homologous serum hepatitis, in addition to the possible effects of excessive volume per se

Reduction of Edema—Therapeutic relief from edema is most efficiently provided when the factors underlying its production are adequately modified Causes

related to lymphatic or venous obstruction, trauma, capillary permeability, increased capillary pressure, and congestive heart failure are not within the scope of the present discussion but must be evaluated before proper therapy can be provided Consideration must be given to multiple factors

Hypoproteinemia may be produced from exogenous or endogenous causes, and massive parenteral therapy directed toward the latter without consideration and care of the former is inefficient Plasma given for hypoproteinemia will only slowly raise total protein levels above the critical minimum for edema at a rate of about 0 1 Gm per cent per unit of administered plasma

The problem of simple overhydration as a cause of edema can readily be met by fluid restriction, but here prevention is a better approach. Water intoxication in patients with renal disease although relatively rare, may be treated in some situations by only minor restriction in fluids or, in the case of anuria may require maintenance by replacement only of fluid lost by insensible routes

Edema caused by sodium retention must be approached in a similar way Therapy aimed at the underlying mechanism of the sodium retention is most important whether this be a simple problem such as excessive sodium intake or a complex situation such as nephrosis Sodium retention may be handled by reduction of sodium intake below excretion Here in addition to dietary regimens which are frequently unpalatable and objectionable, methods to prevent absorption of available sodium are in vogue Excretion of sodium can be hastened by diuretic therapy which brings into use time honored, simple agents and newer, complex, oral and injectable preparations Dialysis and the use of mechanical measures to remove excesses are now mainly limited to research centers with biochemical laboratories of unusual merit Overtreatment with diuretic agents is a hazard that must be guarded against Injectable diuretics may be unnecessary with present oral enzyme system competitors which, with adequate sodium restriction, keep the patient dry This avoids the problem of repeated visits to the physician as well as the danger of local reaction or infection Unsuspected hyponatremia with increasing edema and mental aberrations may develop in the patient on prolonged sodium removal therapy When this condition is present, continued therapy can result in a therapeutic paradox Hypochloremic alkalosis is another clinical complication of overzealous or uncontrolled therapy Observation and reevaluation of the patient are needed to prevent insidious development of these dangers

Restoration of Acid Base Balance—Both metabolic and respiratory acid base disturbances are associated with profound changes in extracellular and intracellular balance as well as with altered renal and extrarenal compensatory mechanisms Complex chemical analyses and calculations as to the alkali reserve the hydrogen ion concentration, body fluid electrolyte pattern and volume give considerable information as to specific losses and therapeutic needs but sometimes fail to provide essential information as to the status of intracellular potassium and intracellular reaction Such a specific need as water replacement may not be suggested by these studies yet demands immediate care Therapy must be based upon fundamental knowledge of the biophysical change and directed toward rational re estab

lishment of the steady state Experience in clinical appraisal of the situation from history and physical examination may be more important than isolated laboratory data. In addition to replacement therapy, the causative factors in production of the depletion must be successfully managed as, for example, the diarrhea of pseudo membranous colitis Intelligent fluid therapy demands evaluation of the whole patient Modification of calculated deficit replacement should be made in the light of such factors as the risk of producing congestive failure and hypertension or the exaggeration of acidosis or circulatory failure

METABOLIC ALKALOSIS —Metabolic alkalosis due to increased alkali intake is relatively rare and may have sodium retention edema as its main feature The chief therapeutic need may be the removal of excess sodium Metabolic alkalosis from acid loss, as seen in severe vomiting or gastric suction with direct loss of chloride anion, requires different replacement therapy from that associated with the potassium loss incident to gastrointestinal damage In situations of potassium deficit, sodium may also be needed although as potassium is replaced intracellularly sodium leaves the cells Hypochloremic alkalosis as sometimes seen in chronic mercurial therapy, may be met by the use of ammonium chloride ammonium chloride is frequently used to potentiate the mercurial effect and may be even considered prophylactic against this type of alkalosis

METABOLIC ACIDOSIS —Metabolic acidosis can be due to ingestion and/or retention of organic acids such as salicylic or boric with resultant decrease in available cations Such cases may need temporary anion relief by means of the artificial kidney Acid retention of diabetes requires proper administration of insulin with precautions to avoid hypoglycemia, as well as replacement of water and sodium Metabolic acidosis of renal failure is associated with alkali loss and retention of fixed anions Cases of acute renal failure may be brought toward normal by the use of such agents as corticosteroids and antibiotics In both acute and chronic renal failure acidosis may be relieved by sodium lactate or bicarbonate, but here the danger of hypertension and vascular overload is considerable, Again temporary use of the artificial kidney may be indicated in anuria caused by acute nephritis or exacerbations of chronic renal disease

RESPIRATORY ALKALOSIS —Respiratory alkalosis related to hyperventilation is best relieved by therapy directed toward the etiology, which may vary from profound psychoneurosis to severe central nervous system trauma Fever, brain tumor or inflammation salicylate therapy or simple habit may be factors Rebreathing or increasing carbon dioxide content of inspired air provides relief

RESPIRATORY ACIDOSIS —Respiratory acidosis caused by chronic pulmonary disease taxes the skill of the most experienced therapist and brings into use digitalization bronchial dilators diuretics antibiotics, corticosteroids, oxygen and even patient re education in the use of accessory respiratory muscles Carbonic anhydrase inhibitors may have some usefulness here The associated hypochloremia and elevated combining power must not be confused with metabolic alkalosis, for the wrong therapy could be fatal Oxygen administration is potentially dangerous as it may produce coma or fatal apnea by relief of the anoxia which in these patients may be the only stimulus to the fatigued respiratory center

AGENTS FOR ADJUSTING AND MAINTAINING INTERNAL HOMEOSTASIS

For Expansion of the Vascular Fluid Volume

Colloidal Fluids.—*For restoration of low blood or plasma volume,* fluids containing colloids have the obvious advantage that they tend to persist longer within the blood vessels than do solutions of crystalloids Hence, the repletion of volume, while by no means permanent, has a duration which is practically satisfactory, requiring a minimum of active interference and a minimum of material Perhaps the most "physiologic" of such replacement fluids are blood and its derivatives

Whole Blood —For replacement of actual blood loss, whole blood affords the most complete answer It is a serious mistake, however, to assume that no other replacement fluid is of real value The greater the depletion of red cell volume, the more urgent is the indication for whole blood transfusion which, at one and the same time, restores both volume and respiratory value to the circulation When blood transfusion is considered primarily for replacement of red cells (i e, when the blood volume is normal in the presence of anemia), one must weigh the possibility of producing a temporary hypervolemia of serious proportions When anemia exists with evidence of vascular engorgement and high plasma volume, the use of packed erythrocytes may be considered The precautions for blood transfusion form a special topic beyond the scope of this discussion

Plasma —In situations where restoration of circulating volume is the primary objective, infusion of plasma (normal human plasma), is as effective as that of whole blood Indeed, there are conditions such as hemoconcentration where, temporarily at least, the introduction of red cells might be considered undesirable The normal plasma proteins insure adequate retention of the fluid in the circulation

Plasma may be more readily available than whole blood because it is more readily preserved especially in the lyophilized form Furthermore, the technique of pooling the plasmas of several donors reduces the probability of agglutination reactions involving the recipient's cells, and typing is not necessary Many clinicians prefer to avoid plasma infusions because of the possibility of transmitting to the patient the virus of serum hepatitis Processing methods have been described which seem practically to eliminate this hazard, but they are not, as yet, generally employed

Plasma Substitutes —The practical disadvantages of plasma for infusion have inspired a continuing search for other colloid materials which might be used in its place Many such substances have been tried, experimentally and in the clinic, and the choice among them is not always clearly defined Each of the plasma substitutes has some potential or actual disadvantage which must be weighed against its possible usefulness in a given clinical situation While studies on experimental animals continue to yield valuable information concerning the virtues as well as the hazards of these materials, such studies indicate significant species differences and have at best only a provisional quantitative applicability to man The necessity for carefully controlled human studies is therefore apparent These are accumulating but are still incomplete

In general, plasma substitutes may be categorized as solutions of protein or solutions of relatively inert, nonprotein material of large molecular size

Protein Solutions Solutions of proteins, provided they are not antigenic, may be employed with excellent results as so called volume expanders In addition solutions of plasma proteins may be used to replace protein deficits Solution of *serum albumin* (normal human serum albumin) of 25 per cent con centration is an excellent volume expander High cost is practically its only disadvantage The danger of serum hepatitis does not exist with this preparation The conventional 25 per cent solution is of course much more concentrated than is the albumin fraction of plasma and has a correspondingly greater restraining power against fluid loss from the circulation Its efficacy as a means of increasing circulatory volume is approximately 5 times that of plasma hence, it must be ad ministered conservatively At the same time it affords an excellent means of in creasing the plasma protein concentration The U S P product is obtained from human blood Purified bovine albumin is available but is sufficiently antigenic that in its present state of development it is best avoided

Modified human globin prepared from red cells discarded in the preparation of plasma has received some attention as a plasma substitute It is administered in 4 or 8 per cent concentration preferably in isotonic saline The material has also great potential value for protein replenishment Further clinical evaluation is required

A rival protein is *gelatin* (gelatin solution special intravenous 6 per cent in isotonic sodium chloride solution) Recent investigations ind cate that this prepara tion may be given safely and satisfactorily for the restoration and maintenance of vascular volume The material is pyrogen free and rarely produces allergic re actions The 6 per cent solution is said to be equivalent volumetrically to plasma D sadvantages include interference with typing and cross matching of the recipi ent s blood and the fact that the solutions gel at room temperature Both of these objections are readily circumvented at least in hospital practice Gelatin of course, is valueless for the purpose of restoring plasma proteins While gelatin may oc casionally produce temporary lesions of renal tubules most human studies indicate that it is not apt to impair renal function

Among many other proteins which have been proposed as plasma substitutes two *modified gelatins* known respectively as *modified fluid gelatin* and *oxypoly-gelatin* show special promise Both of these materials are fluid at ordinary tempera tures Neither has produced clinical reactions attributable to its antigenicity Mod ified fluid gelatin is administered in 3 per cent oxypolygelatin in 5 per cent concen tration in physiologic saline solution It is possible that when controlled by ade quate clinical experience they may be judged as preferable to the parent gelatin

Nonprotein Colloid Solutions Completely removed from the category of ani mal derivatives are certain polymers of high molecular weight which have received intensive scrutiny as plasma substitutes While these materials are quite satisfactory as volume expanders accumulating experience indicates that they are not completely devoid of risk The potential difficulties concern chiefly the blood and the kidneys and the hazards seem to increase with the molecular weight of the polymer and with the frequency of administration

The greatest experience has accrued to the dextrans *Dextran* is a generic term applied to a series of branched polysaccharides composed of glucose units

Commercially, it is prepared from beet sugar by bacterial hydrolysis. The average molecular weight of the marketed product is about 75,000, but each lot represents a spectrum of molecular weights which may be quite broad. A 6 per cent solution in isotonic sodium chloride is recommended as the approximate osmotic equivalent of plasma. Dextran is somewhat antigenic, and a low incidence (under 10 per cent) of allergic reactions may be expected. It seems now to be clearly established that this material, even when used conservatively, may cause prolongation of bleeding time in almost half of the recipients. While clinical bleeding tendency following dextran infusion has been reported relatively rarely, the hazard deserves attention. The mechanism of this hemostatic defect is not known, but some interference with platelet activity has been suggested. The effect is temporary. Coagulation time apparently is not prolonged. Reversible depression of renal tubular function has also been reported in connection with the use of dextran both in animals and in human beings. It is difficult to assess the clinical significance of this observation; obviously the material should be used with caution when kidneys are known to be diseased.

Another useful substance is *polyvinylpyrrolidone* (PVP), a high polymer product obtained from the reaction of ammonia, formaldehyde, and acetylene subjected to high pressure. It appears that polyvinylpyrrolidone may share, perhaps to a less marked degree, the potential disadvantages described for the dextrans. In addition, because of the fact that it is metabolically inert, PVP is known to persist in the tissues for many months following a single infusion. Significant functional defects resulting from such prolonged storage have not been described for human beings. Polyvinylpyrrolidone is used as a 3.5 per cent solution in isotonic sodium chloride.

Russian investigators have reported success with a glucose polymer, *polyglucin*, as a substitute for blood or plasma in the management of traumatic or burn shock. More information is needed about this preparation, but it seems promising.

Solutions of Crystalloids.—Solutions of crystalloids, usually based upon sodium chloride or glucose, have a long and honorable history in the emergency management of reduced blood volume. The poor retention of such solutions within the vascular tree is a notorious disadvantage, but one which may be offset on occasion by the ready availability and general safety of these materials. Their value for repair of the extracellular fluid is considered in another section.

In general, such solutions must be pyrogen free, nontoxic, and approximately isotonic with red cells. Sodium chloride solutions of 0.85 or 0.9 per cent concentration and glucose solutions of 5 per cent are equally efficacious for temporary volume replacement, and the more elaborate solutions, such as Ringer's, Locke's, Tyrode's, and their innumerable modifications, have no special advantage if restoration of volume is the only concern. Because crystalloid solutions leak out of the circulation rapidly, relatively large quantities may be required to restore the circulatory dynamics to normal. For the same reason, these solutions cannot be used with total disregard of the state of the interstitial fluid.

Summary.—The ideal replacement for blood loss is properly matched whole blood. However, it is not always possible or expedient to employ blood where replacement of circulating volume rather than hemoglobin is the immediate concern. Theoretically, at least, plasma would be the ideal solution for such problems were

the possibility of transmitting the virus of hepatitis a negligible factor While plasma substitutes are perhaps physiologically inferior to plasma, they offer the advantages of low cost ease of storage, and freedom from the danger of hepatitis Of the substitutes the colloids are preferable to the crystalloids but the latter should not be forgotten

For Expansion of the Interstitial (Extracellular) Fluid Volume

Clinical situations characterized by volume depletion of the extracellular fluid differ from those considered in the preceding section because as a rule the accompanying low plasma (vascular) volume is not the critical feature While the vascular compartment is depleted along with the interstitial the latter is generally the object of major concern Replacement of extracellular fluid is usually accomplished by the administration of various solutions of crystalloids the choice depending upon the nature of the fluid abnormality i e upon what component of the extracellular fluid is most needed to restore balance In his therapeutic diligence the physician should not forget the virtues of fluids taken by mouth

Isotonic Solutions—Because some salt depletion is always associated with water losses of the magnitude requiring parenteral replacement by far the greatest reliance is placed upon isotonic solutions of the major electrolytes found in the extracellular fluid

ISOTONIC SALINE —The simplest of these is 0.9 per cent sodium chloride solution containing approximately 155 mEq per liter each of Na^+ and Cl^- It will be noted that as the normal levels of Na^+ and Cl^- in extracellular fluid are approximately 142 and 110 mEq per liter, respectively isotonic sodium chloride solution is not ionically perfect neither is it too badly distorted In the presence of normal or at least adequate kidney function there is no cause for concern about the apparent chloride excess The ions being readily diffusible isotonic saline quickly reaches the interstitial fluid when given intravenously It is nonirritating and is therefore equally suitable for subcutaneous administration It is probably the solution of choice for extracellular fluid replacement when (1) there is no reason to suspect marked hypertonicity of the interstitial fluid (2) there is no known or suspected deficit of specific ions such as Ca^{++} or K^+, and (3) there is no serious concern about the acid base balance of the body

BALANCED SOLUTIONS —The more elaborate saline solutions sometimes called balanced solutions reflect an attempt more closely to imitate the chemical anatomy of normal plasma

Ringer's Solution The best known is called Ringer's solution, although very few of the popular varieties follow the original Ringer formula Ringer's solutions contain K^+ and Ca^{++} in addition to Na^+ and Cl^- The potassium and calcium are supplied only in physiologic concentrations which would be ineffective for replacing deficits of these ions

Ringer's solution contains per liter

NaCl	8.6 Gm	(145 mEq each of Na and Cl)
KCl	0.3 Gm	(4 mEq each of K and Cl)
$CaCl_2$	0.33 Gm	(6 mEq each of Ca and Cl)

Lactated Ringer's Solution. "Plain Ringer's" fluids of the type just described contain more chloride than does the normal extracellular fluid and, while electrically neutral, tend to have a slight acidifying effect in the body. There is some theoretical justification, therefore, for including an excess of sodium over chloride, as is done in lactated Ringer's solution, which has the following composition per liter:

NaCl	6.0 Gm.	(103 mEq. each of Na^+ and Cl^-)
KCl	0.3 Gm.	(4 mEq. each of K^+ and Cl^-)
$CaCl_2$	0.2 Gm.	(3.6 mEq. each of Ca^{++} and Cl^-)
Na lactate	3.1 Gm.	(27.7 mEq. each of Na^+ and lactate)

ISOTONIC DEXTROSE.—Isotonic dextrose solution (dextrose injection 5 per cent) is recommended where 'pure water deficiency' is thought to exist. In such cases, there is evidence that water loss has greatly exceeded salt loss, with resulting hypertonicity of the tissue fluids, and electrolyte replacement is not indicated. So far as the electrolytes of extracellular fluid are concerned, the dextrose solution has the effect of a hypotonic replacement fluid.

DEXTROSE AND SODIUM CHLORIDE.—Isotonic solutions are frequently employed as the vehicles for specific substances which one desires to introduce. The combination of 0.9 per cent sodium chloride with appropriate amounts of glucose, potassium chloride, calcium chloride, sodium bicarbonate, etc., is a very common and accepted practice. A favorite formula for rehydration in the presence of salt loss is 5 per cent glucose in 0.9 per cent sodium chloride solution (dextrose and sodium chloride injection). While this solution is not isotonic with red cells, the electrolyte effect on extracellular fluids is the same as with ordinary isotonic saline solution, and the glucose has some value as a nutrient.

Hypertonic Solutions.—Where salt has been lost in excess of water, replacement of the electrolytes is indicated. For this purpose, hypertonic solutions may be employed. A 3 per cent sodium chloride solution, containing 513 mEq. each of Na^+ and Cl^-, is recommended. Stronger solutions of sodium chloride may be used but the concentration should not exceed 5 per cent.

For the Reduction of Interstitial or Intracellular Volume

Greater difficulty may be encountered in the removal of excesses of water or of retained electrolytes than in the replacement of deficits. This is due in part to the difficulty of assessing clinically the cause of the fluid retention as well as to the multitude of available agents. Edema due to cardiac failure per se does not fall within the scope of this discussion, and cardiovascular agents and diuretics which are essential in this area are discussed elsewhere (Chapter 5). Fluid accumulation may also be related to inflammation or allergy, venous or lymphatic obstruction, or nutritional disturbance. The problem of colloid osmotic pressure, capillary blood pressure, and hypoproteinemia has been discussed; as regards the renal factor, retention of water and sodium chloride is of prime importance. For this reason, measures aimed at water or sodium depletion are used. In some instances, as in the nephritic, water retention may be due to simple water overload. Here water intake, which includes all dietary water, may need to be drastically reduced so as to balance that excreted. Success here may depend upon less than 0.5 liter difference per day.

Increase in Salt Excretion—Agents used to increase renal excretion of sodium and chloride include the various diuretic preparations presented elsewhere (Chapter 5) Several deserve repeated mention

WATER DIURESIS—Water diuresis, while favorably reported by some, has potential danger In theory patients who have excesses of electrolytes may have fluid depletion In such patients, water administration, either orally or parenterally, results in decreased tubular resorption as well as increased glomerular filtration and excretion of the excessive sodium However, many subjects do not have this relative fluid deficit, and water administration results in severe intoxication

MERCURIAL DIURETICS—Mercurial diuretics remain among the most effective agents, particularly when used parenterally and with ammonium chloride The effect is attributed to the inability of the tubules to reabsorb sodium and chloride in the presence of mercury Decreased effectiveness in the presence of hypochloremic alkalosis suggests that the main action may be upon the chloride ion rather than upon sodium

CARBONIC ANHYDRASE INHIBITORS—Carbonic anhydrase inhibitors are currently popular clinically, and new preparations are frequent in this group They are often ineffective for therapy of the acute condition but useful to keep the patient edema free after adequate treatment with other agents

THIAZIDE DERIVATIVES—Chlorothiazide hydrochlorothiazide flumethiazide and associated substances are thought to have diuretic action resembling a combination of carbonic anhydrase inhibition as well as mercurial like blockage of sodium chloride resorption Great usefulness of these preparations is related to oral effectiveness and minor toxicity

UREA—Urea remains an effective diuretic when given in daily doses of 40 to 50 Gm as a 40 per cent solution in water or carbonated beverages Success requires raising the nonprotein nitrogen to 80 to 90 mg per 100 ml, which causes an increased urine flow and salt loss by interfering with filtrate reabsorption

Removal of Salt From Gastrointestinal Tract—Depletion of sodium by way of the gastrointestinal tract has been attempted for years, with unpredictable and usually unsuccessful results, by the use of severe catharsis, continuous colonic irrigation or intestinal lavage A more effective approach is the sodium binding action of the cation exchange resins which prevents intestinal transfer of the cation and results in fecal elimination Dialysis by means of the artificial kidney is another method of removing sodium when the kidney has temporarily lost its excretory function

Salt Restriction—Restriction of dietary sodium chloride gives variable results depending upon such factors as previous excesses, the degree of renal or cardiac improvement afforded by other measures, and the adjuvant use of active methods to facilitate sodium excretion

For Adjustment of Ionic Balance

Therapy for adjusting ionic balance must be guided by consideration of the multiple regulatory mechanisms of the body and the fact that one area of deficit cannot be adjusted without alterations of intra- and extracellular fluid volume,

concentration, ion ratio, and even distribution of the ion deficit being corrected Undue burden must not be placed on the regulatory mechanisms themselves lest replacement cause even more deficit Since the amount of the deficiency is not accurately known, the therapist must cautiously and gradually attempt replacement, frequently assessing the clinical status to ensure that a therapeutic paradox has not resulted With the exception of conditions such as intestinal obstruction or surgery, severe nausea, vomiting, or hemorrhage, the oral administration of ions for replacement is preferred over the parenteral route The latter has definite disadvantages, such as the possible production of pyrogenic reactions or circulatory insufficiency

Sodium Depletion —

ISOTONIC SALINE —Isotonic sodium chloride solution is a time honored replacement fluid and has been previously discussed In addition to providing sodium it is excellent for replacement of body water, particularly when kidney function does not create a potential problem in sodium retention Sodium chloride is potentially an acidifying salt In the majority of instances of sodium depletion, 0 9 per cent sodium chloride solution would appear to be the agent of choice It must be given in amounts adequate to replace the sodium deficiency with care not to disturb volume

HYPERTONIC SALINE —Hypertonic sodium chloride solution may be indicated in advanced extracellular sodium depletion Care must be exercised at all times to avoid overloading hypertension, and congestive failure Total quantity as well as speed of administration must be considered Use should perhaps be restricted to cases where dehydration is not a problem as a concentrating effect is desired In some instances it may even be desirable to restrict water Prepared solutions vary in concentration from 2 to 5 per cent A greater hazard is associated with the more concentrated solutions

HYPOTONIC SALINE WITH DEXTROSE —Hypotonic sodium chloride solution with dextrose is an efficient agent to replace water and maintain sodium at normal levels For continued parenteral fluid therapy, it is prophylactic in that it provides water and also sodium in quantity sufficient neither to overload nor to diminish extracellular content Commercially available solutions contain 0 425 per cent sodium chloride and 2 5 per cent dextrose

ORAL SALT REPLACEMENT —Oral agents to replenish sodium loss may be given as simple oral milk feedings or by intubation with constant drip through a small plastic tube Isotonic sodium chloride solution or a saline solution, made by dissolving 5 Gm of sodium chloride (1 large teaspoonful) and 2 5 Gm of sodium bicarbonate in 1 000 ml of water, may be administered in this way Enteric coated tablets of sodium chloride are available, but even when taken with large quantities of water they frequently produce nausea and vomiting

Potassium Depletion —With all preparations of potassium, the danger of hyperkalemia is present Even small amounts of potassium by mouth may be catastrophic in the presence of kidney failure

POTASSIUM CHLORIDE —Potassium chloride is the most commonly used preparation at present It may be obtained commercially in the concentration of 80 mEq of potassium per liter in 5 per cent dextrose, or in half normal sodium chloride

solution. Vials containing 20 ml. of sterile 15 per cent potassium chloride solution are available commercially; each vial contains 40 mEq. of potassium. These vials may be added to proper solutions of sodium chloride or dextrose to produce excellent replacement solutions. Unless the potassium deficit is severe, replacement can be obtained with less danger of cardiac arrest by using concentrations of 40 mEq. per liter. When concentrations of 80 mEq. per liter are used, the rate of injection should not exceed 10 ml. per minute. When potassium is being replaced intracellularly, the simultaneous use of sodium chloride carries a potential danger of increasing the potassium deficit because the administered sodium may enter the cells more readily than the administered potassium.

Potassium Phosphate.—Potassium phosphate solution is commonly prepared by the addition of a commercially available ampule (20 ml. containing 60 mEq. of potassium) to 1,000 ml. of 5 per cent dextrose, which results in a buffered solution at a relatively safe concentration. Some authorities feel that this preparation is to be preferred for specific intracellular potassium deficiency not associated with alkalosis, since the potassium is supplied with its usual intracellular anion.

Potassium Acetate.—Potassium acetate solutions may be prepared by adding 1 or 2 ampules (20 ml. containing 40 mEq. of potassium) to 1,000 ml. of 5 per cent dextrose solution. This solution has the advantage in acidosis with retention of phosphate or chloride ions of providing potassium with an anion that can be easily metabolized.

Balanced Solutions.—

Darrow's Solution. Balanced electrolyte solutions are typified by Darrow's solution, which contains in each liter:

KCl	2.7 Gm.	(35 mEq. each of K and Cl)
NaCl	4.0 Gm.	(69 mEq. each of Na and Cl)
Na lactate	4.4 Gm.	(53 mEq. each of Na and lactate)

This preparation is used particularly in the treatment of infantile diarrhea associated with metabolic acidosis and intracellular potassium deficiency.

Elkinton's Solution. A high potassium, low sodium solution designed by Elkinton is useful in therapy of metabolic alkalosis associated with intracellular potassium deficiency. This solution contains in each liter:

K_2HPO_4	3.2 Gm.	(37 mEq. each of K and HPO)
KH_2PO	0.7 Gm.	(5 mEq. each of K and H_2PO)
KCl	3.0 Gm.	(40 mEq. each of K and Cl)
NaCl	4.2 Gm.	(72 mEq. each of Na and Cl)

Elkinton's solution may be approximated by adding 60 mEq. of buffered potassium phosphate and 80 mEq. of potassium chloride to 1 liter of isotonic sodium chloride and 1 liter of 5 per cent dextrose in water. The low sodium content of this solution may facilitate the replacement of the abnormal intracellular sodium by the administered potassium.

Incorporation of serum proteins in a balanced solution of electrolytes has been recommended recently for extracellular fluid repair, especially in pediatric practice.

Oral Potassium Replacement.—Oral potassium preparations are available which supply potassium as chloride or gluconate in liquid or tablet form. Fruit

juices generally are high in potassium and provide an excellent vehicle for even additional amounts of potassium chloride, *with the exception of tomato juice they* are very low in sodium Dialyzed milk is also high in potassium and relatively low in sodium

Calcium Deficiency —Abnormalities in calcium metabolism are related to vari *ations in absorption,* distribution and excretion of this cation Regulation of these factors is very complex and involves diet, renal function, parathyroid activity, the state of the gastrointestinal tract, and the acid base balance of the body Tetany due to hypocalcemia may be associated with low intake of calcium and/or vitamin D, hypoparathyroidism intestinal diseases, as sprue, with low assimilation of cal cium, increased serum alkalinity from any cause including hyperventilation and excesses of certain chemicals such as citrates and phosphates

Calcium Gluconate —Calcium gluconate (9 0 per cent calcium) may be given by oral intramuscular, or intravenous routes, the latter being the most com mon Sterile 10 per cent solution is available commercially, and this concentration may be given slowly by vein or even intramuscularly The intramuscular route has the disadvantage of local irritation To make a 0 3 per cent solution which can be administered slowly for prolonged effect 30 ml of 10 per cent solution may be diluted in 1,000 ml of isotonic saline

Calcium Chloride —Calcium chloride (27 per cent calcium) is freely soluble in water and is used commonly for oral administration *It is locally irritating* and should not be injected into tissues If given intravenously, the concentration should not exceed 5 per cent of the salt, and the rate should be less than 2 ml per minute *in order to avoid systolic cardiac arrest Orally the average daily dose is about 8* Gm , milk is a good vehicle The acidifying nature of the chloride may support the calcium effect against tetany

Calcium Lactate —Calcium lactate (13 per cent calcium) is an excellent preparation for oral calcium administration and is well tolerated As much as 4 Gm daily may be administered

Calcium Phosphate —Dibasic calcium phosphate and tribasic calcium phos phate may be useful as antacids but also serve to supply calcium and phosphorus The total daily dose is 8 Gm Mixtures of the dibasic phosphate and gluconate are frequently used as antepartum dietary supplements, vitamin D in varying amounts is incorporated in many of these preparations

Calcium Carbonate —Precipitated calcium carbonate (40 per cent calcium) is suitable only for oral use It serves as a gastric antacid and may be converted into a soluble salt with consequent absorption in the lower bowel

Magnesium Abnormalities —Although magnesium is an important cation in intracellular metabolism, little is known specifically about its quantitative relation ships Magnesium deficits are associated with chronic renal disease and massive diuresis Symptoms and signs are described as hyperirritability, nausea, vomiting convulsions and tetany Magnesium excess is associated with advanced renal dis ease and decreased urine output Central nervous system depression, with stupor and hyporeflexia, is an important manifestation

Magnesium Sulfate —Magnesium sulfate is commonly used parenterally by slow *intravenous administration* of 10 ml of 25 per cent solution, the 20 or 25 per

cent solutions may also be given intramuscularly Magnesium is employed in the management of eclamptic convulsions seizures related to local cerebral edema, tetanus, and other states which call for depression of the central nervous system Duration of action is short, and small repeated doses may be indicated

Occasionally, the inclusion of magnesium in therapy directed toward restoration of fluid balance has resulted in dramatic improvement in the clinical state, but the indications for such therapy are not clearly defined

For Adjustment of Acid Base Balance

In the treatment of acidosis or alkalosis one may have to give attention to specific ion adjustments as well as to the more general problem of body reaction For example metabolic acidosis may be associated with sodium depletion or hyperchloremia requiring special attention in the therapeutic plan

Acidosis.—

Isotonic Sodium Lactate Solution —Isotonic sodium lactate solution ($\frac{1}{6}$ molar) provides the necessary sodium for combination with bicarbonate in acidosis The lactate is readily metabolized to provide energy This is true for levorotatory sodium lactate, but commercial racemic preparations may be excreted before the metabolic effect takes place Sodium lactate solutions are not affected by boiling or high temperatures Vials of hypertonic solution are also available and may be used to prepare isotonic solutions by appropriate dilution

Hypertonic Sodium Lactate Solution —Hypertonic sodium lactate solution (molar) may be used in cases of severe acidosis when body water is not depleted and fluid restriction may be desirable Here great care must be observed to prevent vascular overload the usual commercially available solutions must be diluted with at least equal parts of water before use

Isotonic Sodium Bicarbonate Solution —Isotonic sodium bicarbonate solution (1 3 per cent) is available commercially Sterilization of the solution may drive off important quantities of carbon dioxide Again isotonic solutions may be prepared by dilution of the hypertonic solution The usefulness of bicarbonate in therapy of acidosis can be questioned on the basis that low HCO_3 is related to retention of fixed anion rather than to a true deficit or unavailability of the bicarbonate

Hypertonic Sodium Bicarbonate Solution —Hypertonic sodium bicarbonate solution is available in vials containing 40 mEq These vials may be added to other solutions to obtain the desired concentration of sodium bicarbonate. The prepared 7 5 per cent solution of sodium bicarbonate must be diluted with equal parts or more of water before administration This form again has the advantage of an alkalizing action when fluid intake is markedly restricted It must be given slowly because of the danger of producing hypertension and congestive failure

Sodium Bicarbonate Oral.—Oral agents for therapy of systemic acidosis include sodium bicarbonate tablets Since metabolic acidosis is a problem in volume, composition and acid base balance oral medication usually is less effective than parenteral therapy By the time oral agents can be tolerated, the acidosis usually has been well compensated

Alkalosis —

AMMONIUM CHLORIDE SOLUTION —Ammonium chloride solution (2 per cent) may be used in patients with severe alkalosis due to specific chloride loss, as in pyloric stenosis With liver and kidney disease the organism may not be able to dispose of or metabolize the ammonium ion, so alkalosis in this type of patient is best treated by other means Ammonium chloride, 1/6 molar, in isotonic saline solution, may be a safer form for parenteral administration This is also a hypertonic solution, but with conversion of NH_4^+ to urea it is isotonic in effect

AMMONIUM CHLORIDE, ORAL —Ammonium chloride enteric coated tablets (0 5 Gm) may be considered prophylactic acidifiers when used in conjunction with mercurial diuretics Here disproportionate chloride loss could result in therapeutic alkalosis

DESIGN FOR USE OF AGENTS FOR ADJUSTING AND MAINTAINING INTERNAL HOMEOSTASIS

While fluid and electrolyte replacement therapy is not an exact science, the best results are obtained with the least danger when some rational plan is followed As with other forms of treatment, a reasonably accurate estimate of the clinical situation is a necessary prerequisite Three types of information should be sought (1) evidence that a threat to internal homeostasis does in fact exist, (2) the nature of the defect or excess, (3) roughly, the amount of the defect or excess Four types of abnormalities may be encountered, involving (1) volume, (2) osmotic relationships (3) specific ions, and (4) acid base relationships Two or more of these categories may and often do exist simultaneously

Fluid Therapy

Estimate of the Fluid Imbalance —

ABNORMALITIES OF VOLUME —In practice, decision as to the presence of a significant volume defect is largely one of clinical judgment It is possible, of course, to estimate plasma and extracellular fluid volumes by special laboratory procedures However, such estimates are costly, time consuming, and sufficiently inconvenient to place them among the tools of the investigator rather than the practitioner Fortunately, the clinical features of overhydration and underhydration are a sufficiently safe guide in most instances A careful history and a painstaking physical examination will usually permit a fairly shrewd guess, not only as to the existence of a volume abnormality but also as to its nature and extent

Among the simpler and more rapid laboratory tests, some reliance may be placed upon the hematocrit and upon the color and specific gravity of the urine (the latter provided renal function may be assumed as approximately normal) Hemoconcentration usually points to a volume deficit, though there are some striking exceptions The same is true of elevated plasma protein concentration (rapidly estimated from the specific gravity of properly collected plasma or serum) Similarly, scanty urine of high color and high specific gravity is suggestive of dehydration However, none of these indices has any real quantitative significance If one has prior knowledge of the patient, changes in body weight may afford important clues as to massive gain or loss of water

Since a quantitative estimate of volume abnormality is difficult to achieve simply and rapidly, a practically useful first approximation may be obtained from the following rough relationships (Hardy)

Mild dehydration	volume deficit 4 per cent of body weight
Moderate dehydration	volume deficit 6 per cent of body weight
Severe dehydration	volume deficit 8 per cent of body weight

The degree of dehydration is based upon clinical observation, and the tentative estimate of fluid deficit is made accordingly

OSMOTIC ABNORMALITIES —When the body loses markedly hypotonic or hypertonic fluids in large volumes, the remaining extracellular fluid is left with an excess or deficit of dissolved material, and the normal osmotic relationships between cells and their environment are disturbed This condition leads to hydration or dehydration of the intracellular fluid and perhaps to other cellular changes as well While osmotic defects may often be inferred from purely clinical data, the definitive diagnosis rests upon the chemical analysis of plasma

While the total electrolyte concentration of plasma, which must be accepted as an index to the state of the interstitial fluid as well, is normally about 310 mEq per liter (155 mEq each of cations and anions), it is not necessary to make a complete chemical analysis of plasma in order to divine the presence of osmolar abnormalities In fact, a very reliable decision on this point requires only two relatively simple determinations, namely, plasma chloride and plasma bicarbonate, the latter being estimated from the carbon dioxide-combining power of the plasma If the sum of Cl and HCO_3^-, the most labile of the plasma anions, lies between 125 and 135 mEq per liter, the total osmolarity of the plasma (and interstitial fluid) may be considered within normal limits The average normal sum is 130 mEq per liter (Table 3) Plasma sodium gives valuable confirmatory information, but this analysis may not be readily available The normal Na^+ of plasma is close to 142 mEq per liter Since Na^+ is the chief cation of extracellular fluid, its concentration is significant with respect to total ion concentration

ABNORMALITIES OF SPECIFIC IONS —The electrolyte structure of extracellular fluid is based upon Na^+, Cl^-, and HCO_3^- However, there are other important ions to which attention must frequently be directed Of these, K^+ and Ca^{++} are perhaps the most troublesome Adequate chemical methods are available for their estimation, and no other method for detecting abnormalities of these materials is at all reliable It is rarely necessary to analyze for Mg^{++}

*Table 3 Normal Electrolyte Pattern of Plasma**

Cations	mEq/Liter	Anions	mEq/Liter
Na^+	142	Cl	103
K^+	5	HCO_3	27
Ca^{++}	5	HPO_4	2
Mg^{++}	3	SO_4	1
		Organic Acids	6
		Protein	16
Totals	155		155

*After Gamble, J L Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Harvard University Press, 1949

ACID BASE BALANCE—The only certain method of diagnosing disturbances of the acid base balance is by measuring the pH of the blood This is frequently awkward or impractical, and in untrained hands may give very misleading results Besides owing to the efficiency of the blood buffers, the pH may be within normal limits when the buffer systems themselves are nearly exhausted Inferences regarding the acid base balance of the body may be drawn from the clinical examination together with certain aspects of the blood chemistry

As indicated in the introductory section, blood pH may be calculated from analysis for HCO_3 and for H_2CO_3 However, these observations require that the blood samples be handled anaerobically, a matter simpler in theory than in practice Hence, the more crude and incomplete carbon dioxide combining power of plasma (or serum) is still applied extensively to the problem With all of its admitted faults, this method gives information of value

The carbon dioxide combining power affords an estimate of plasma bicarbonate under conditions of "physiologic" carbon dioxide tension (about 40 mm Hg) Indirectly, this quantity reflects the amount of plasma cation not already combined with or matched by anions of acids stronger than carbonic, i e, the amount available for immediate neutralization of strong acids Obviously, this measurement does not include all of the blood buffers Furthermore, it neutralizes short term effects of respiration upon the anion distribution in the plasma

The average normal carbon dioxide combining power of plasma is about 60 volumes per cent, representing 27 mEq of HCO_3^- per liter (To convert volumes per cent CO_2 into milliequivalents of HCO_3 per liter of plasma, divide the former by 2 22) In general, values less than 20 mEq per liter indicate a significant trend toward acidosis, while values above 30 mEq per liter have the opposite implication There are important exceptions Hyperventilation may induce alkalosis with *low* plasma bicarbonate secondary to excessive pulmonary excretion of carbon dioxide In such cases, compensatory mechanisms include renal excretion of sodium while chloride is retained, and the latter component of plasma is elevated Conversely inadequate pulmonary ventilation leads to so called respiratory acidosis, with retention of carbon dioxide, *elevated* plasma bicarbonate, and depressed levels of plasma chloride For these reasons, respiratory function must always be considered in the interpretation of plasma electrolyte concentrations

*Table 4 Conversion of Gravimetric Concentrations of Plasma Electrolytes to Combining Equivalents**

Element	Atomic Weight	Conversion Factor (mg % × Factor = mEq/Liter)
Na	23	0 435
K	39	0 256
Ca	40	0 500
Mg	24	0 833
Cl	35	0 286

*One equivalent (= 1 000 milliequivalents) is equal to 1 gram atomic weight divided by the valence The general formula for conversion of mg per cent to mEq per liter is

$$\text{mEq per liter} = \frac{\text{mg per cent} \times 10 \times \text{valence}}{\text{atomic weight}}$$

Plan of Therapy—It has been emphasized that fluid therapy should be systematic and tailored to the specific indications presented by the patient This does not mean that treatment must be delayed until the laboratory reports are available In fact, one may institute therapy based upon the clinical state alone and make later modifications according to clinical response and laboratory data

A safe general rule is to direct initial therapy toward volume replacement There are several reasons for the recommended starting point *First*, volume deficit, especially if severe, imposes a very serious physiologic strain upon the organism and cries for immediate correction *Second*, a satisfactory approximation of the volume deficit can be made from clinical observation, and no harm can result from immediate administration of isotonic fluids *Third*, the initial laboratory data may fail to reveal specific ion deficits because they are masked by hemoconcentration, while excesses will be corrected by volume replacement Finally, in adults at least, the body buffers will frequently be adequate for correction of acid base imbalance once the volume and osmolarity of the body fluids are brought within normal limits

If an early decision can be made regarding osmotic abnormalities, their correction can be incorporated with the adjustment of fluid volume Osmotic imbalance may be strongly suggested by the history In any event, the chloride and bicarbonate concentrations of plasma may be ascertained before volume replacement has progressed very far and from these an estimate of osmolar deficiency or excess is available as indicated in a preceding section As volume correction continues, additional analyses of blood and urine will dictate whether or not measures should be taken to correct abnormalities of specific ions or of fluid reaction

Estimating requirements prior to the beginning of treatment is at best a form of guessing Hence, therapy must be controlled as it progresses and modified accordingly If the conservative plan of slight undercorrection is followed at each stage of treatment, the necessary modifications are readily made One must expect that the correction of severe fluid imbalance will require several days For following the progress of therapy, primary reliance is once more upon the clinical response of the patient However, this should be supported by periodic laboratory studies so that one may know whether the treatment is actually accomplishing what is intended Eventually, a regimen must be established which will maintain internal homeostasis Data obtained during the active correction of abnormalities will indicate what one may expect from the patient's physiologic mechanisms and will be generally helpful in devising a maintenance schedule

It has been assumed in this discussion that fluids are to be administered parenterally The necessity for good products (free from pyrogens and bacterial contamination) and for good technique is obvious and will not be considered further A few precautions may be worthy of summary In general, intravenous infusions should be given slowly, particularly if they contain colloids It is difficult to be specific on this point because there are wide differences among patients as to tolerance and among solutions as to the actual risks involved However, barring those situations in which a rapid repletion of blood volume is essential to restore circulation there seems to be little indication for haste in administration, and a rate of 1 liter per hour should rarely be exceeded For large volume deficits, a much slower rate, say 250 ml per hour, is preferable There is much merit in the recommenda

tion (Hardy) that the entire estimated requirement for the 24 hour period be administered during the usual waking hours as a continuous infusion Special care must be exercised when therapeutic concentrations of potassium are administered Potassium in high concentration is very toxic to the heart and should be infused slowly and under constant supervision Calcium, on the other hand may be administered with much less danger of untoward effect If markedly hypertonic solutions are indicated, they must be given by vein because they are irritating and their introduction into the tissues may cause sloughing Markedly hypotonic solutions should not be administered parenterally

Control of Fluid Excess

The same type of information should be sought for proper therapy of excesses in fluid volume as for replacement of deficits New drugs for removing excess body water are appearing constantly However, restriction of water intake is frequently the proper course, particularly in the semianuric patient or in those subjected to zealous overtreatment with parenteral fluids

Restriction of sodium or use of the multitude of agents advocated to aid in its excretion should not be considered until all possible causes for edema and hypotonicity have been investigated Relief of fluid excess may depend upon correction of hypoproteinemia secondary to liver disease, kidney damage, or improper nutrition Similarly, one must be careful about treating hypotonicity by the administration of sodium chloride unless salt depletion is truly present Otherwise, the use of sodium chloride particularly hypertonic sodium chloride may be harmful Sodium depletion or water intoxication should be confirmed before sodium chloride is given in such instances

Control of Electrolyte Excess

Sodium and chloride excess can be treated by decreasing the intake of these substances or by aiding their renal and/or extrarenal excretion This type of control is essentially the therapy of congestive heart failure and is presented elsewhere It includes restriction of sodium, removal by dialysis or exchange resins, and forced excretion by the use of diuretics

Excess of potassium, as manifested by increased concentration in extracellular fluid, presents serious problems in control and, if not corrected, may result in cardiac standstill. These excesses may be treated by any or all of the following methods

1 Where hyperkalemia is associated with water loss expansion of the volume of body fluids by the administration of fluids which contain no potassium is effective

2 Removal of extracellular potassium may be accomplished by a number of processes including intracellular transfer Here therapy of existing dehydration or abnormal carbohydrate metabolism is important Potassium may also be removed by improving urinary excretion Proper treatment of any cause of impaired renal function as congestive failure or kidney disease, is of course, essential Similarly, potassium may be removed by gastrointestinal and/or peritoneal lavage, by exchange resins, and by the use of the artificial kidney The latter method is con

stantly being improved, and its use, while now restricted, may soon become commonplace

3 Antagonism of potassium may be attempted by the use of calcium salts and digitalis Sodium chloride may also be considered an antagonist but is less beneficial in this respect The use of potassium in treating digitalis toxicity is probably more effective than the reverse

In summary, excess of electrolytes can be treated by restriction of intake and by attempts to increase excretion Potassium excesses are poorly withstood by the body and their excretion or transfer must be promptly undertaken In cases of temporary loss of excretory ability, vivodialysis should be considered

RATIONAL BASIS FOR NEW AGENTS FOR ADJUSTING AND MAINTAINING INTERNAL HOMEOSTASIS

Blood and Plasma Substitutes—It is generally agreed that all currently available blood and plasma substitutes are inferior to the natural material The criteria for an ideal volume expander have been repeatedly stated, but in essence they amount to a description of the properties of plasma What is needed is a material which maintains increased circulatory volume for an extended period, but which has no immediate or remote ill effects upon the organism Low cost, ready availability, uniformity, and stability in storage are important additional considerations

Since blood and plasma must always be obtained from human donors, they will probably never be available in unlimited quantities, and stockpiling for war or disaster would remain a problem even if the materials could be stored indefinitely However, extension of the useful life of bank blood is worthy of continued serious study As for plasma, the lyophilized product keeps well, and the logical goal would seem to be a sure way to inactivate the virus of hepatitis without rendering the plasma unsuitable in other respects

Regardless of progress, or the lack thereof, toward the objectives just mentioned, search for better plasma substitutes than are now at hand will undoubtedly continue if only because one cannot visualize having a comfortable supply of plasma Since there are satisfactory substitutes, the need is perhaps not critical, but one would like to hope for nonantigenic and otherwise nontoxic synthetic or semisynthetic colloids which approach the plasma proteins not only in their oncotic properties but in their metabolic behavior

Repair and Replacement Fluids—In the area of materials for replacement or adjustment of body fluids the need would appear to be for improved methods of assessing the chemical status of the patient rather than for better correctional agents Where fluid imbalance results from endocrine imbalance, as is the case with diabetes mellitus or Addison s disease cheaper, safer, and more efficient drugs to combat the underlying metabolic lesion may of course, be envisioned

Drugs—Recent biophysical investigations have resulted in better understanding of the mechanisms which control fluid balance This is especially true in relation to the corticosteroids and their effects on metabolism As more information is obtained regarding the role of hormones in controlling fluid balance, congestive failure, hypertension, and kidney function newer preparations in this area may be expected These preparations may be of prophylactic value rather than specifically

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curative in effect At present, aldosterone and its antagonists, as well as serotonin, are undergoing extensive study Enzyme systems and their controls are fertile areas for new preparations for control of the internal environment

SELECTED REFERENCES

Adolph, E F The Metabolism and Distribution of Water in Body and Tissues, Physiol Rev 13 336, 1933

Bard, Philip Medical Physiology, St Louis, 1956, The C V Mosby Co, pp 332 339, 743 779, 808 810

Bland, J H The Clinical Use of Fluid and Electrolyte, Philadelphia, 1952, W B Saunders Co

Danowski, T S, and Elkinton, J R Exchanges of Potassium Related to Organs and Systems, Pharmacol Rev 3 42, 1951

Darrow, D C, and Pratt, E L Fluid Therapy, Relation to Tissue Composition and the Expenditure of Water and Electrolyte, J A M A 143 365, 1950

Drill, V A Pharmacology in Medicine, A Collaborative Textbook, New York, 1958, McGraw-Hill Book Co, pp 535 618

Elkinton, J R, and Danowski, T S The Body Fluids, Baltimore, 1955, Williams & Wilkins Co

Goodman, [illegible] f Therapeutics, New York, [illegible]

Guyton, [illegible] 1956, W B Saunders Co, [illegible]

Gamble, [illegible] Extracellular Fluid, Cam[illegible]

Gropper, [illegible] Expanders, Internat Abstr Surg 95 321, 1952

Hardy, J D Fluid Therapy, Philadelphia, 1954, Lea & Febiger

Mollison, P L Blood Transfusion in Clinical Medicine, Springfield, Ill, 1956, Charles C Thomas, Publisher

Moyer, C A Fluid Balance, A Clinical Manual, Chicago, 1952, The Year Book Publishers, Inc

Overman, R R Sodium, Potassium and Chloride Alterations in Disease, Physiol Rev 31 285, 1951

Schmidt, [illegible] Transport and Regulation of Calcium, [illegible] 15 297, 1935

Sjostrand [illegible] cance in Regulating the [illegible]

Technical [illegible] epartment of Commerce, No 67020 1955

Weisberg, H F Water, Electrolyte and Acid Base Balance, Baltimore, 1953, Williams & Wilkins Co

Wiggers C J The Physiology of Shock, New York, 1950, Commonwealth Fund

THE CHOICE OF A DIURETIC

Walter Modell, M D.

INTRODUCTION

Reviews have appeared from time to time in an attempt to summarize a mountainous literature on diuretics, and of a large list the reader is referred to a full historical and clinical account by Vogl, one on the more technical aspects of diuretics by Pitts and Sartorius and one on the more recent literature by Modell The clinical experiences and the several drugs which are available or under investigation will be considered separately

The diuretics are discussed in this unconventional position in a systematized consideration of drugs and their therapeutic uses to emphasize their fundamental therapeutic function which, as indicated in the preceding chapter is, in fact, to relieve symptoms due to internal derangements of electrolyte and fluid Their more obvious effect of increasing the rate of urine flow is actually the consequence of their tendency to rearrange internal electrolyte relationships The urgently needed therapeutic effect of improving the excretory function of a failing kidney or increasing the rate of excretion of toxic materials in poisoning is so rarely an attribute of these drugs which superficially seem to stimulate renal activity as to be an outstanding therapeutic paradox

There are, of course a number of clinical conditions in which their pharmacologic actions are useful Of these, the relief of the edema, particularly that of congestive heart failure, is by far the most important They are also used in the ascites of cirrhosis, the nephrotic syndrome, and the edema of pregnancy Glaucoma, hyperpotassemia, bromide intoxication, the anginal syndrome, epilepsy, migraine, hypertension, and premenstrual depression provide highly specialized uses for diuretics in conditions in which edema is not present or at least not definitely established Despite the apparent dissimilarity of these conditions, in all the usefulness of the diuretic as a therapeutic agent depends on its capacity to rearrange internal water and electrolyte relationships

CLINICAL APPLICATIONS

Edema

The edema of heart disease provides the most important use for diuretic agents The practice has been to reserve diuretics for severe cases of congestive failure in

which digitalis is insufficient There is clinical evidence, however, that some diuretics provide relief *more promptly and are more dependable* than digitalis, and as a result there is an increasing tendency to use diuretics along with digitalis at the outset of treatment

Although diuretics are used with good results in what are commonly designated the right sided and the left sided forms of heart failure and the regimens for treatment are much the same, indications and urgency are often quite different and the character of action and result are also *somewhat different* Separate discussion is therefore profitable

Right-Sided Heart Failure—This form is the more commonly recognized manifestation of heart failure even though there is reason to believe that the left sided form may be an equally frequent, or even the more frequent, clinical syndrome The difference in rate of recognition may be largely due to the fact that the signs of right sided failure are easily noticed since they are largely external, being expressed as ankle edema which mounts up the legs and thighs, with characteristic *pitting quality* *In this situation a large diuresis, sometimes inducing a loss of 10* pounds or more overnight, is an emphatic demonstration to patient and physician of the need and utility of a diuretic The question of the need for treatment of the edema rarely arises in this situation, more often the only question is that of the choice of the diuretic to be used in those cases in which digitalis alone is not sufficiently effective

Left Sided Heart Failure—This form of cardiac edema provides much more subtle indic [illegible] is far less frequently [illegible] of the pulmonary be [illegible] uch cases, only those clinicians who are willing to rest their case entirely on symptoms—dyspnea on exertion, modest orthopnea, angina decubitus—will see the indication for diuretics

That the use of such potent diuretics as the mercurials may produce only a modest diuresis also tends to weaken the faith of some in the existence of edema or the propriety of the therapy Yet in a large number of cases with hypertension or mitral stenosis, the subsequent development of full blown signs of left sided heart failure will provide the proof that the initial symptoms without detectable signs were the forerunners of the later unmistakable developments The fact remains that clinically imperceptible amounts of fluid in the pulmonary bed, in the interstitial spaces rather than in the alveoli, may interfere perceptibly with respiration There is the additional fact that when this fluid is removed by the action of diuretics, the very small diuresis provides great relief and comfort, significantly increases the ability of the patient to perform, and often effectively prevents the subsequent development of pulmonary edema This early subtle form of left sided heart failure tends to be overlooked and untreated while the full fledged forms of pulmonary edema usually present no question of the need for treatment

The mercurial diuretics have long been recognized as of outstanding value in the treatment and prophylaxis of frank pulmonary edema, paroxysmal nocturnal dyspnea, etc, but, *unfortunately*, less commonly for the earlier stages Even for the patient with only dyspnea on effort and no râles, the mercurials, rather than

less potent diuretics, are more likely to provide a large measure of relief and to be the most effective in prophylaxis

Angina Decubitus.—The relief provided by mercurial diuretics to patients with the anginal syndrome, especially angina decubitus, a manifestation of left sided heart failure, was reported by Gold some years ago and has since been confirmed by others Further experience is necessary to establish criteria for the selection of suitable patients with the anginal syndrome for this treatment Until then, the only patients with anginal pain for whom this form of therapy can be prescribed with reasonable assurance of benefit are those with angina decubitus

Pulmonary Disease.—In chronic pulmonary disease of a variety of types, cor pulmonale may result It has been suggested that in those cases with respiratory acidosis and congestive heart failure, there may be a large diuretic response to acetazolamide (and presumably, the other carbonic anhydrase inhibitors) and a salutary effect on accumulated plasma bicarbonate which makes it the diuretic of preference in this highly specialized type of edema

Refractory Edema of Heart Disease.—This is a term with inconstant implications, changing largely in inverse relation to the effectiveness of measures applied With the advent of modern diuretics, the incidence of refractory edema has diminished markedly Recently refractory cardiac edema was defined as that which a daily routine of 2 ml doses of mercurial diuretics together with digitalis and salt-poor diet failed to relieve By such standards Rubin and associates state that it now occurs in less than 1 per cent of patients with congestive heart failure

Aminophylline.—Vogl and Esserman claim that the addition of aminophylline to a regimen with mercurial diuretics is useful in "intractable" failure Their use of the term is inappropriate for they admit that "complete lack of response to mercurial diuretics has never been demonstrated" Their data show that the patients in their study were inadequately treated with mercurial diuretics The utility of the method requires confirmation

Exchange Resins.—There is the suggestion in the literature that the resins may act to potentiate mercurial diuretics especially in those cases in which a hydrogen exchange resin is used to the extent of inducing a degree of hyperchloremic acidosis The degree to which this method is useful has not yet been established, but there are significant implications in the fact that the use of the resins has tended to decrease with the increase in experience with them

Ammonium Chloride.—Ammonium chloride may synergize with mercurial diuretics, and the statement has been made that it may reverse refractory heart failure due to hypochloremia However much ammonium chloride may assist in the action of the mercurial diuretics it does not appear to provide a consistent answer to the problem of resistance to them

Acetazolamide (Diamox).—Rubin and associates used Diamox in the management of edema refractory to mercurial diuretics but found that only after it was combined with relatively large doses of ammonium chloride, so that a degree of hyperchloremic acidosis developed was the lost vigor restored to the mercurials These findings probably apply also to the more recently introduced carbonic anhydrase inhibitors

ACTH and Cortisone.—The late Dr Schemm and his co-workers described cases of otherwise refractory edema in which, following the use of corticotropin

(ACTH) and cortisone, sodium excretion and diuresis returned spontaneously in some while in others there was restored responsiveness to mercurial diuretics The authors were unable to describe the type of patient with resistant edema who is likely to respond to this form of therapy This paradoxical phenomenon lacks not only explanation but also confirmation It is possible however, that recent findings of materials which antagonize aldosterone have some bearing on it

Peritoneal Dialysis—Leiter describes peritoneal dialysis as a means of removing sodium This procedure is followed by diuresis in some patients with resistant cardiac edema, but the physical factors involved in its application seem to have limited its utilization

Southey Tubes—A plea for the use of this device has been made by Fiese and Thayer, who claim that it is more sound physiologically than diuretics in that it removes edema per se and does not act through the diuresis of a particular electrolyte There is the possibility, however that should it be used more extensively electrolyte disturbances would develop in some cases just as they do after paracentesis

Diet—Diets with low salt content have long been used in combination with diuretics, especially for resistant cases Iseri and associates have described satisfactory results in this state with diets containing as little as 50 mg of sodium The Council on Food and Nutrition of the American Medical Association has issued a warning about the possibilities of salt depletion syndromes resulting from such diets in combination with potent diuretic agents

Nephrotic Syndrome—Since the report in 1941 by Tyson of fatalities following the use of mercurial diuretics in children with the nephrotic syndrome this condition has been an accepted contraindication to their use even though the danger has not been confirmed by others As a consequence little is to be found in the recent literature on the utility of the mercurial diuretics in this condition

ACTH and Cortisone—Good results in the therapy of the nephrotic syndrome with these agents have been reported by many Some argue that in many cases in which diuresis is induced there are signs of improvement in renal function along with the relief of edema and that this may well indicate a salutary effect on the basic disease process Striking improvements are often short lived and sometimes associated with disagreeable or more serious reactions Some writers express doubt as to whether the ultimate course of the syndrome is permanently or significantly influenced by this therapy

Resins—There are reports that the exchange resins may remove edema in the nephrotic syndrome, but there are also warnings against the possibility of electrolyte disturbance and the induction of other forms of renal dysfunction

Albumin—Concentrated human albumin especially salt poor serum albumin produces a diuresis in patients with the nephrotic syndrome but there is no evidence that this alters the glomerular filtration rate or the eventual course of the disease

Cirrhotic Edema—The edema of cirrhosis chiefly ascites has been relatively resistant to diuretic therapy, and a specialized mechanism of edema formation has been suggested There is some question regarding the practical value of diuretics in cirrhosis and as matters stand none of our current therapies appears to be either potent or uniformly effective in this condition

On the other hand sodium is retained with this form of edema and any device which produces a negative sodium balance will to a degree, cause a diuresis Rigid restriction of sodium in the diet is said to result in protein sparing reduced rate of ascites formation, and reduced need for abdominal tapping Hilton states that patients with cirrhosis who fail to respond to the mercurial diuretics often exhibit satisfactory results if ammonium chloride is given along with it Salt poor albumin in conjunction with the mercurial diuretics and low sodium diet have also been shown to be effective Others have reported diuresis after the exchange resins, but opinion on their utility is mixed

Edema of Pregnancy—Salt poor albumin has been reported to relieve edema in patients with toxemia of pregnancy Brown and Sutherland state that ammonium chloride produced increases in sodium excretion with relief of the edema and other symptoms of pregnancy While mercurials were even more effective these authors suggest caution when they are used during pregnancy

Removal of Nonedematous Fluid

Glaucoma —Carbonic anhydrase facilitates the formation of intraocular fluid and therefore it is not surprising that acetazolamide and the newer carbonic anhydrase inhibitors ethoxzolamide and dichlorphenamide were found to lower intraocular pressure in glaucoma Both oral and intravenous administration are effective but there is no report on local application Some state that the effect on intraocular pressure is short lived and that refractoriness soon develops The best results which may sometimes be dramatic are more likely to occur in acute glaucoma while protracted therapy for chronic glaucoma is apt to be uncertain Supplemental use of miotic drugs is suggested

Electrolyte Derangements

Hypo and Hyperpotassemia —Exchange resins have been suggested as the basis of the treatment of hypo and hyperpotassemia although no reports of their successful use in the clinical conditions have been made Because it accelerates potassium excretion Diamox has been suggested for hyperpotassemia More recently dichlorphenamide a new carbonic anhydrase inhibitor has been used to treat respiratory acidosis

Bromide Intoxication —In 1941 Bodansky and Modell reported that mercurial and xanthine diuretics markedly accelerated the renal excretion of the bromide ion This finding has been successfully applied to the treatment of bromide poisoning

Unknown Mechanism of Action

Hypertension —It is held by some that the removal of sodium stores has a beneficial effect on the course of hypertension A treatment for hypertension based on this hypothesis has been described in which diuretics are used to accelerate the excretion of sodium It must be added that whereas this has not been confirmed it may also have a bearing on the established effectiveness of chlorothiazide in hypertension See Chapter 25 for further details

Epilepsy—Bergstrom and associates and Merlis report diminution of epileptic seizures with the use of acetazolamide (Diamox), but the former suggest that this action of drug is of limited value No adequate explanation has yet been offered for this effect

Migraine—*Foldes* recently reported on an antiretentional therapy' for migraine in which he postulated cerebral edema and for which he suggests that diuretic therapy can be used for both prophylaxis and treatment This novel concept is without confirmation

Premenstrual Tension—The demonstration of premenstrual retention of salt and water has led to trial of salt restriction as well as diuretics It is difficult to distinguish between pharmacodynamic and psychologic aspects of relief in this condition and a well controlled study is needed to establish diuresis as a useful therapy for premenstrual tension

THE PHARMACOLOGIC BASIS OF DIURETIC THERAPY

Diuretic drugs are almost always used for the removal of extracellular fluid Regardless of the nature or the site of their action, if diuretics are to accomplish this they must induce a negative sodium balance Since this action is never specific for sodium alone but to a varying degree involves other ions as well diuresis also constitutes a variable threat to electrolyte homeostasis It appears not to matter greatly what the precise nature of the diuretic device is, restriction of sodium in the diet mercury inhibiting salt resorption in the renal tubule, acetazolamide depressing hydration of carbon dioxide exchange resins drawing salt from the food in the intestinal tract or water diuresis all may and sometimes do induce clinically evident electrolyte disturbances Combinations of these devices are even more likely to do this Electrolyte disturbances have also been reported after paracentesis It is interesting to note that there is now evidence suggesting that the too free use of water together with potent diuretics may be an important cause of electrolyte disturbances

Dangers of Diuretic Therapy—The two major dangers of diuretic therapy are electrolyte disturbances and toxic reactions due to the specific nature of the drugs rather than as a consequence of diuresis That a threat to electrolyte homeostasis is inherent in the mechanism of effective diuresis has already been explained The danger is a real one only in so far as the therapist fails to recognize this quality of the diuretic procedure The danger of specific drug intoxication from the diuretic is a possibility of course, as with all drugs Since this is an individual matter, it will be considered in relation to the particular agents in the appropriate sections

Reaction of the prostate, with acute prostatic shutdown due to excessive diuresis is a danger which should be considered before the regimen is written for the elderly male patient

THE DIURETICS

Diet

Diet affects the flow of urine for precisely the same reason as most diuretics namely there is diuresis to the degree that the restriction of sodium intake results

in a negative sodium balance This physiologic fact was recognized more than 75 years ago Its recent resurgence comes as part of a routine rather than as the sole measure in the treatment of edema. Occasionally however one may observe a satisfactory diuresis produced by salt restriction alone

The choice of the patient in whom dietary restriction alone is likely to be a practical measure may be based on the difference it makes in his sodium balance This depends largely on two factors (1) the customary salt intake of the patient and (2) the rate at which his kidney excretes sodium

Whereas the average American consumes about 10 Gm of salt daily, there are many who customarily take considerably more and in the latter the restriction of salt is more likely to induce significant alterations in salt balance It is a practical matter, therefore to examine the patient s usual diet carefully and to base one s anticipation on it The ability of the kidney to excrete salt is, to a degree also reflected in the relation of edema accumulation to the patient s customary diet Should a patient accumulate edema on a relatively low salt intake, it indicates markedly reduced renal capacity for salt elimination and while salt restriction is also ind cated it does not offer much hope that this measure alone even though very stringently applied will be especially effective in reducing edema. Details and explanations of thi limitation are to be found in an excellent review by Danowski

The chief disadvantage of the low salt regimen is its impalatability for most patients Early willingness to cooperate often quickly changes to obstinate resistance and unfortunately there are no safe and satisfactorily salty salt substitutes

The Karell diet as modified by Gold or 2 quarts of milk as the sole article of the diet with an equal amount of water daily contains a bit more than 2 Gm of salt It is not therefore unusually low in sodium content Others have used diets containing as little as 50 mg of sodium daily and the rice diet recommended by Kempner contains about 150 mg of sodium The virtues of the milk diet are convenience and assurance milk is one of the easiest articles of diet to get under any circumstances No cook or restaurateur is likely to add salt to it its salt content is never likely to exceed that provided by the cow It is the item of food par excellence therefore for those who use the restaurant as well as for the emergency situation The unopened egg is likewise an article of diet to which it may safely be assumed that no salt has been added

Under all but carefully controlled conditions it must be assumed no matter how vigorous the denials that a so-called low salt diet contains approximately the same amount of salt as the average d et supplied by the same purveyor of food This negative attitude is based on unhappy experiences that led me to doubt my best friends under this particular set of circumstances But it is one which leads to better results in the therapy of edema

Water

Water as the basis of a systematic treatment of edema was reintroduced by Schemm in 1942 Water diuresis is not a self limiting process and like other diuretics when used excessively may induce hyponatremia and tissue dehydration

The case for water as a clinical diuretic reposes on what may well be called

the demonstration of a feat by Schemm, namely, that considerable amounts of edema can be removed by large amounts of water, i e, from 6 to 8 liters daily, especially when the diet has an acid ash The practical limitations of such a dreary method are obvious Perhaps the major contribution of this demonstration of the diuretic capacity of water is that it has emphasized the undesirability of limiting water intake of patients with edema It should also be recalled that excessive use of water together with diuretics has been implicated as a cause of serious electrolyte unbalance

It must be pointed out, also, that there are areas in this country in which tap water contains so much sodium that it may aggravate the dropsical state of the patient with heart disease

Ammonium Chloride

Ammonium chloride has been used in the treatment of edema for its own diuretic action as well as for its enhancement of the action of the mercurial and xanthine diuretics Within a few days after ammonium chloride is administered, it becomes ineffective as a diuretic Despite this self-limiting protective device to conserve base, ammonium chloride may sometimes cause acidosis

The enhancement of the mercurial diuretics is a more practical action It has been shown that 8 Gm of ammonium chloride given for 2 days may double the effect of Mercuhydrin in some cases This action appears to be more useful when smaller doses of the mercurial are used than with the usual 2 ml doses This has variously been attributed to the effect of relative acidosis and the influence of the chloride ion

Ammonium nitrate and calcium chloride, acid forming diuretics with much the same uses and limitations, are less frequently used A recent paper by Luckey and his co workers suggests, however, that there are instances of ammonia intoxication after ammonium chloride which can be prevented by the use of calcium chloride

Osmotic Diuretics

The use of osmotic diuretics, e g, urea, has declined steadily since the advent of new, modern, more potent, and more dependable diuretics Older work has indicated that while these agents may induce a degree of salt loss, as a rule this is not very large, and the diuresis, beyond that induced by the water ingested along with the osmotic agent, is very small indeed Inasmuch as salt retention is the major problem in most instances in which diuretics are required, these observations provide little incentive for a search for new osmotic diuretics

Xanthine Diuretics

Although drugs of this large group have long been known to exhibit diuretic activity and are still widely used for this purpose, their position in the therapy of edema is definitely secondary to that of the mercurials Special merits, in addition to their diuretic action, have been attached by some to the xanthines in the treatment of congestive heart failure, although this is not supported by proof Investi-

gations on the effect of aminophylline on the cerebral circulation have indicated that therapeutic doses in man may cause constriction of the cerebral vessels and a degree of cerebral anoxia Gastrointestinal distress is very common after the oral use of all xanthine diuretics

Vogl and Esserman recommend aminophylline as a supplement to mercury diuretics in intractable congestive heart failure, but a study in which the combination was subjected to precise measurements does not support this contention

Administration —Studies have shown that the rectal retention enema is the most effective nonparenteral route of administration of xanthine diuretics There are wide variations in blood levels after the administration of tablets and suppositories Others also have found the oral route less effective than the parenteral, while, by the intramuscular route, aminophylline produced local discomfort

Newer Xanthine Diuretics —Whereas Pearson reported it to be a feeble diuretic, Choledyl (choline theophyllinate) has been recommended by others for the treatment of congestive heart failure as well as for the anginal syndrome Negligible gastrointestinal irritation has been claimed and these claims have provided material for a polemic in the columns of the *Journal of the American Medical Association*

Summary —The reasons for the present inferior position of the xanthine drugs in the therapy of edema may be briefly listed (1) They are not as effective as the mercurials (2) They are not as dependable as the mercurials (3) Given by mouth, effective doses cause a high incidence of gastrointestinal distress and are relatively ineffectual, nor is this materially improved when similar doses are given by suppository (4) When they are given intravenously, fatalities as well as less serious immediate reactions have been reported (5) When they are given intramuscularly local discomfort is common These considerations do not, however vitiate whatever uses they may exert due to other pharmacodynamic actions which they possess

Mercurial Diuretics

In a recent editorial, the mercurial diuretics were called "the greatest advance in the treatment of chronic congestive failure since Withering" There are suggestions that in the relief of some aspects of cardiac edema they may sometimes surpass digitalis as well as all other diuretics now in common use Despite publication of an increasing number of toxic reactions, the mercurial diuretics retain their position of pre eminence and, as a matter of fact their use has increased through introduction of new forms and the extension of therapeutic usefulness to such important areas as the prophylaxis of pulmonary edema, asthma complicated by heart disease, cirrhosis of the liver, and bromide poisoning The experience of most physicians with these agents in the treatment of cardiac edema is so large and general that it will not be reviewed here

Untoward Reactions —The older literature contains many accounts of patients who have received several hundreds of injections of mercurial diuretics without special incident or renal injury and with long continued effectiveness There are also patients who have reacted badly, some after the first dose of the mercurials, but in most instances after a period of salutary results In view of the potency of

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the drugs as well as their wide scale use, this is not surprising Since the reactio to mercurials have already been well described, the present account will consid only briefly statements in the literature which appear to add something to the a ready well known picture

DIGITALIS REINTOXICATION—There is the now almost classic view that whe mercurial diuretics act to release large amounts of fluid locked in the tissue inte spaces, there is also liberated such digitalis as may have been fixed in the fluid, ar that in the already well digitalized patient, this supplement of digitalis may som times be sufficient to induce symptoms of digitalis intoxication This view, hov ever attractive or presumably reasonable, has never been supported by substanti evidence It may now be assumed that the *coup de grâce* was delivered by a pul lication by St George et al These investigators demonstrated that the digitoxi content in edema fluids of well digitalized patients with ascites or pleural effusior was so small that redigitalization through its mobilization is not conceivable

ELECTROLYTE DISTURBANCES—Because of an increased interest in problems c electrolyte balance as well as the fact that the mercurial diuretics have bee combined with devices for enhancing the negative sodium balance and have bee used with increasing vigor in resistant cases, electrolyte disturbances have attracte the greatest part of the recent attention devoted to diuretic reactions Sever varieties of electrolyte disturbance have been described hypochloremic alkalosi hypopotassemic alkalosis hyponatremia with hypervolemia and with hypovolemi

OTHER REACTIONS—Brown has reviewed the subject of reactions to mercuria diuretics and has grouped them into toxic and allergic reactions In addition t the symptoms attributable to electrolyte disturbances, he lists chills, fever, malaise muscular aching, nausea erythema, chest pain, vomiting dyspnea, tetany, an allergic reactions

PREVENTION OF REACTIONS—Means of avoiding reactions is a matter of som interest Caution has been advised against the excessive use of mercurials in gen eral and more specifically against excessive diuresis Modell has shown that muscle cramps developing after the use of mercurial diuretics may be correlated directly with the extent of diuresis and, presumably, transient electrolyte imbalance, rather than with the dose of mercury injected, and also that a diuresis which exceeds tha producing a weight loss of 2 pounds markedly increases the incidence of cramps

Skin Tests Brown points out that skin tests are usually of little value in avoiding reactions Patients who have a history of allergic reaction to some mercurial diuretics may tolerate others, but this is not invariably the case Where previous allergic reactions have been severe, recourse to another type of diuretic is the safest procedure

Specific Antidotes A few specific methods of combating toxicity of mercurials have been suggested While dimercaprol (BAL) has been shown clearly to reduce the acute toxicity of the mercurials, there is no good evidence that this also applies to the later toxic effects in which the concentration of mercury in the tissues is very low The fact that latent reactions occur after mercaptomerin, a monothiol, also suggests that the dithiol BAL may be of little value in this respect Magnesium sulfate to prevent ventricular fibrillation has been reported as useless The hope that ascorbic acid might provide an antidote has not been substantiated by clinical trials

Cohn reports that some symptoms of hypersensitivity can be prevented by the concomitant use of antihistamine drugs

Mode of Administration Fatality after the intravenous injection of mercurial diuretics is now unheard of largely it may be assumed, because that route has been abandoned in favor of the intramuscular While the latter is unquestionably the safer, there seems to be no reason why in a hypersensitive patient serious reaction or fatality may not develop after mercurials are injected into the muscle

Mercury Resistance —Responsiveness to the organic mercurials sometimes decreases significantly after a longer or shorter period of satisfactory reactivity Rarely is mercury resistance encountered at the outset of the use of the organic mercurials and absolute pharmacologic tolerance may be considered outside the range of normal variability More often than not clinical resistance develops in urgently ill patients A variety of circumstances especially electrolyte disturbances have been examined and suggested as an explanation for this state

Sometimes but not invariably ammonium chloride will restore responsiveness which continues for a period and once more ammonium chloride is needed Diamox and ammonium or calcium chloride comprise the most recent attack on the problem and a favorable report is considered in more detail in another section as is the suggestion that aminophylline is a most effective agent A recent report that pyridoxine may be used to overcome mercury fastness lacks confirmation as well as basis

Self Administration —Self administration of diuretics is economically desirable for the patient and also makes possible an ideal in treatment—the daily balancing of water and salt metabolism

Subcutaneous —There are reports of the satisfactory subcutaneous self administration of mercaptomerin and of meralluride Mergamate is another mercurial recently reported as effective and satisfactory by subcutaneous injection Confirmation is awaited

Rectal —Salyrgan (mersalyl) and Mercuzanthin (mercurophylline) were administered in suppository form in previous years but were discontinued largely because of a high incidence of proctitis Reports on satisfactory results with Mercuhydrin suppositories without rectal or colonic reactions have not been confirmed by a substantial experience

Oral —Whereas all organic mercurials have long been known to be effective when administered by mouth there are sharp limitations to this convenient route of administration due mainly to a high incidence of distressing symptoms, especially the gastrointestinal In this connection it is well to recall that most bioassays of the potency of the oral diuretics in man consider only diuretic potency and fail to take into account undesirable effects in the gastrointestinal tract which develop only after continued use

Neohydrin (Chlormerodrin) At the time of this writing this drug is the most widely used oral mercurial diuretic Good results as well as economic advantages have been reported but such good results are not obtained in severe cases There are also reports of gastric distress from continued use

Mercurital and Merpurate These are reported to be effective oral diuretics able to replace parenteral therapy completely However, information is not avail

able concerning the extent of congestive failure in the patients or the duration of treatment or development of toxicity

Newer Mercurial Diuretics.—

MERCAPTOMERIN (DIUCARDYN, THIOMERIN) —The introduction of a mono *thiol group* into an organic mercurial seems not to interfere significantly with diuretic potency of, at least some, mercurial diuretics e g , mercaptomerin, whereas it reduces acute cardiac toxicity and local irritant action and therefore, may be administered subcutaneously Satisfactory clinical results with mercaptomerin in the treatment of congestive heart failure have been reported by many

The question which needs to be settled is whether mercaptomerin is superior to the standard mercurials in terms of reduction of toxic reactions There are clinical reports that mercaptomerin is not without disadvantages but there are yet no clear statements of clinical superiority or inferiority to the other established organic mercurials The best evidence indicates that they are all of about equal potency *and tendency to latent reaction* Mercaptomerin does have the advantage of subcutaneous acceptability

DICURIN (MERETHOXYLLINE) —*This drug* has been introduced *recently* and is usually sold in a mixture containing procaine It appears to be about as effective as most of the mercurial diuretics now on the market, but statements of lessened *irritativeness must be considered not yet established*

CUMERTILIN (MERCUMATILIN) —This has been reported to be about as effective by parenteral injection as others in common use and to be potent orally as well as intramuscularly

Summary —The mercurial diuretics are the injectable diuretics of choice since *they are the most potent as well as the most dependable* *Their toxicity is not an* important consideration either by comparison with other diuretics or in relation to the seriousness of the conditions in which they provide such excellent relief Those now on the market differ little from one another and there appears *to be slight* basis for special preference other than that of local reaction Unfortunately, the oral and rectal preparations have not answered the problem of self-administration for patients who require mercurial diuretics, a compromise solution is provided by the subcutaneous administration of mercaptomerin and meralluride

Exchange Resins

Although it has long been used in industry, the principle of ion exchange has been applied only recently to the treatment of edema The attractiveness of the concept of removing the salt from the diet after the palate has been satisfied, the early reports of minimal toxicity, the desire *for a substitute* for the salt poor diet and a complement to mercurial diuretics led to widespread trial As a result of these trials however the drugs are far less used than when first introduced

Types —There
changers, which rer
exchangers the sulf
use The first is the more strongly acid and the
carboxylic resins have the greater capacity for exchange in the medium existing in the gastrointestinal tract Diverse opinions *will be found with no* large body of

the resin to remove sodium from the intestinal tract is considerably decreased when the salt *ingested is limited*, yet the low salt diet cannot be avoided because the exchanger can rarely be taken in amounts large enough to produce a useful effect with average salt ingestion Thus the resins turn out to be a nearly complete failure, they have not served to eliminate the nuisance and tastelessness of the usual salt poor cardiac diet and at the same time, they are far less effective than the standard diuretics As a result, the exchange *resin plays a minor role in the therapy* of edema Special indications for the resins, such as the treatment of hypo- and *hyperpotassemia may provide a continuing* use for them

Carbonic Anhydrase Inhibitors

Acetazolamide (Diamox) and Its Congeners —Although there are now a large number of drugs which are known to inhibit the activity of carbonic anhydrase only one acetazolamide (Diamox), *has been widely used as a diuretic* At the time of this writing other carbonic anhydrase inhibitors belonging to the *same chemical series as Diamox* are under active investigation Dirnate has been reported to be too feeble to be of real value Dichlorphenamide (Daranide) and ethoxzolamide (Cardrase) have been recently introduced into the commercial drug market but do not appear to have any special advantages over Diamox The subject of carbonic anhydrase inhibition is relatively new and is being actively investigated It may be assumed that many views now expressed will be modified

What can be said of Diamox applies to the other carbonic anhydrase inhibitors now available The *extent to which carbonic anhydrase inhibition develops depends* on the dose and the concentration of Diamox in the plasma However, there are sharp limitations to the diuretic action of Diamox When Diamox is given around the clock or in large single daily doses, alkalinization of the urine and diuresis ceases after 3 to 4 days The daily ceiling dose has been established to be approximately 500 mg On the other hand doses smaller than 250 mg per day are not likely to be effective by mouth although they may be so when given intravenously

The action of carbonic anhydrase is not restricted to the renal tubule for it is a ubiquitous enzyme whose functions in all the tissues in which it is found are not *understood No organ or tissue has been shown to have a* special affinity for the inhibitor and effects exerted elsewhere than on the kidney are now being studied The utility of Diamox in glaucoma *through decrease in intraocular fluid formation* and in epilepsy through an ill understood mechanism, are discussed in another section Effects on pancreatic secretion, saliva the cerebrospinal fluid, and red blood cells have not as yet been demonstrated to have any clinical importance

Effect on Electrolyte Balance —The development of Diamox action is followed *by a rise in urinary pH* with increased excretion of bicarbonate, sodium and potassium and a decrease in chloride and ammonia excretion, and titratable acidity of the urine There appears to be little change in phosphate excretion When these electrolyte alterations are uncompensated hyperchloremic acidosis develops

Schwartz and Relman reported that Diamox is not likely to cause serious acidosis because its effect on serum bicarbonate tends *to limit its ability to increase* the excretion of base A self limiting action has also been reported by others who

opinion preponderantly supporting the clinical utility or preferability of either the sulfonic or the carboxylic resin, nor have combinations of carboxylic and sulfonic resins proved particularly advantageous

The nonspecific character of cation exchange results in removal of other ions than sodium, potassium in particular, and, to overcome this, exchangers have been made which release potassium This combination, unfortunately, still further decreases the sodium removal capacity of the exchangers and provides a new danger, that of hyperpotassemia Depletion of calcium and magnesium is also possible, but usually minimal, so that no addition of these minerals is made to the exchangers Dock and Frank point out that there is, nevertheless, a distinct risk of gradual demineralization of bone in patients on a steady diet of exchangers over a period of years They mention two cases of tetany

At present, the most acceptable resins are mixtures of ammonium or hydrogen exchangers with potassium exchangers in a 2 1 or 3 1 ratio Mixtures of anion and cation exchange resins have been suggested for special instances, such as renal disease

Effects on Electrolyte Balance —The fundamental action of the resin, to exchange one ion for another, is, unfortunately, not highly selective, and ions removed as well as those provided in exchange may cause disturbances of electrolyte homeostasis There is the possibility of producing hyperchloremic acidosis as well as hypopotassemia Some discount the importance of such possibilities, pointing out that adaptive reactions of the intestinal tract prevent the depletion of sodium by the resins, that there is no evidence of depletion of sodium stores through the continued use of the resins and that the fecal sodium excretion diminishes with the continued use of resins Coincidentally with this, however, there is a tendency for fecal potassium to increase and, in patients receiving the resins for prolonged periods, for the potassium removed to exceed that of the sodium Danowski and associates state that after 6 months' use there may be danger of hyponatremia and hypocalcemia They believe that if the resins are to be effective, liberalization of the diet is not possible and that prolonged therapy may lead also to potassium deficit and acidosis Others report negative sodium balance in patients on low sodium diet and a tendency to hyperchloremic acidosis which is greater in renal disease

Other Toxic Effects Casts have been found in the urine of patients without renal insufficiency, which led to a warning regarding their use in renal disease of any severity

It has been said that patients with severe hepatic disease tolerate the resins poorly Highly specialized toxic effects have been reported in patients with cirrhosis drowsiness, apathy weakness slurring of speech, disorientation, and tremor

Summary —The theoretic advantages of the cation exchange resins are often overbalanced by realistic disadvantages such as impotence, necessitating large doses and rigid salt restriction for significant effects unpleasant texture, making ingestion of the necessary large amounts difficult and irritant action, making gastrointestinal difficulties common after usage The addition of potassium decreases the likelihood of hypopotassemia but considerably decreases exchange effectiveness The ability of

ACTH and Cortisone

The action of ACTH and cortisone derivatives to induce diuresis has alrea been discussed in the sections on refractory cardiac edema and the treatment the nephrotic syndrome

Chlorothiazide (Diuril) and Its Congeners

Chlorothiazide is attracting more attention in the current literature, medic seminars and symposia than any other recent diuretic If everything claimed f it is true it is a major addition to the drugs available for cardiovascular disease well as for all forms of edema This orally effective agent is now recommended a diuretic A discussion of the use of this drug in the treatment of hypertensio will be found in Chapter 25 Whereas other newer drugs closely related to are now in use there is no evidence that they are pharmacologically different ar for that reason chlorothiazide the best known member will be discussed as th prototype

It is perhaps important to emphasize at this point that most of the statemen of its actions and effects uses and lack of danger come as the result of studies cor ducted by investigators in selected rather than the usual run of cases It has bee made available on the commercial drug market only recently so that there are fe published experiences on its effects uses, or dangers in the hands of the practitione This statement is not made to dampen interest in an extremely interesting agen If the drug proves to be as effective in the hands of the practitioner as it seems t be in the minds of its promoters, it will easily survive this expression of the nee for caution The statement is made merely to prevent the disaster that befal useful drugs which are introduced on the heels of exaggerated claims and which because they fail to live up to them are dismissed as entirely without merit It is I think, permissible to repeat at this time, when there seems to be almost nothin but unequivocal enthusiasm for chlorothiazide, that the true utility of a drug ca be determined and its proper exploitation developed only after the broad experi ence made possible by general use, and, further, that the full potential for dange of drugs is usually not established until after several years of trial With these basic reservations it is only fair to state my opinion that chlorothiazide not only i a most interesting diuretic but also appears to have advantages over all other ora diuretics now in use

The mode of action of chlorothiazide is unique in that it exerts two actions, each characteristic of an entirely different type of diuretic On the one hand, it has potent carbonic anhydrase activity and therefore, acts in the same way as acetazolamide (Diamox) and, on the other hand like mercurial diuretics it acts directly on the renal tubule to depress salt resorption, although on a different transport system This combination of actions seems to have a peculiar advantage in that the tendency of the former to retain chloride and lose bicarbonate leading to hyperchloremic acidosis is cancelled by the latter action which induces chloride loss and otherwise leads to hypochloremic alkalosis

The drug is well absorbed from the gastrointestinal tract and is commonly given orally in doses of 0 5 Gm twice a day The effects of such doses develop quickly and disappear almost completely within 12 to 15 hours

found that despite continued use, diuresis soon diminishes and within 2 to 5 days urine returns to its pretreatment composition, and, in addition, this corresponds with the appearance of hyperchloremia The action of Diamox to increase potassium excretion has led to the suggestion that it be used in hyperpotassemia

TOXIC REACTIONS —Serious toxic reactions thus far have been relatively rare In those subjects with renal disease and acidosis Diamox seems to be without much effect The earliest reports contained accounts of paresthesias, lassitude and drowsiness These symptoms usually disappear even though the drug is continued Although carbonic anhydrase inhibition produces hyperchloremic acidosis and accelerates the excretion of potassium serious reactions due to this action are uncommon in man apparently because of the self limiting nature of the drug Febrile reactions have been reported

The close chemical relationship of Diamox and the sulfonamides suggest the possibility of related toxic reactions At this early date in the clinical experience with Diamox cases of agranulocytosis renal lesions similar to those after sulfonamides, and thrombocytopenia have already been published

SUMMARY —Friedberg and associates and others report a satisfactory experience with Diamox in patients with congestive failure On the other hand Relman and co workers were disappointed because half of their patients failed to lose edema Diamox is not as potent as the mercurial diuretics nor can it be substituted for them It is an effective oral diuretic however and may be used as an adjunct to the mercurial diuretics Because of its self limiting action, Diamox is usually given for 2 or 3 days and discontinued for the remainder of the week to permit readjustment of electrolyte and restoration of activity At the present time there is no evidence of superiority of any of the three available drugs of this series Cardrase Diamox and Daranide The differences in absolute potency can be made up by adjustment in dosage so that for all practical purposes they are equally useful

Methazolamide (Neptazane) —In view of the current and growing interest in the extreme effectiveness of chlorothiazide and its many effective new congeners by the oral route interest in the carbonic anhydrase inhibitors in the treatment of edema has subsided considerably whereas the interest in their utility in glaucoma has grown substantially Thus there is a new carbonic anhydrase inhibitor methazolamide (Neptazane) which undoubtedly has the diuretic actions of the others but which is advertised only for its utility in glaucoma

Pyrimidine Dione or Amino Uracil Diuretics

A number of amino uracil also called pyrimidine dione drugs exert diuretic activity when given by mouth Some members of the amino uracil group are also strongly emetic One member of this group Mictine (aminometradine), has been reported to be significantly less emetic than others in the group It is a relatively feeble diuretic but clinical experience with the drug is still too small to evaluate its position as an oral material Rolicton (amisometradine), a new Mictine like drug is too recent an addition for comment other than that there is yet no evidence of superiority over Mictine despite the fact that Rolicton was introduced to replace Mictine The general impression however, is that it is a relatively feeble diuretic

Combinations

Combinations of diuretic devices are used either because the edema attacked is relatively resistant to any one measure or because the urgency of the situation calls for relatively rapid relief It is to be borne in mind that the continued use of combined measures to increase and prolong the negative salt balance is the more likely therapy to induce electrolyte disturbance syndromes It is essential, therefore, that the combination of measures used to relieve edema be altered as the nature and extent of the edema alters and responds to the treatment, and that blood electrolyte levels be followed as therapy progresses

New Diuretics Under Investigation

It is perhaps of more than passing interest that an ability to exert a diuresis has recently been added to the multitudinous pharmacologic accomplishments of the so called tranquilizer, chlorpromazine (Thorazine) How this action is developed is not clear nor is its record as a clinical diuretic outstanding Other phenothiazine congeners remain to be tested, and until there is a clear picture of their clinical value as diuretics no recommendation regarding their use can be made

Perhaps the most exciting new possibility is an entirely new approach to the problem that of aldosterone inhibition There is evidence that spirolactone, an aldosterone like structure antagonizes the action of aldosterone on sodium resorption in the renal tubule The first clinical trials with spirolactone indicate that it also induces diuresis in patients with edema At this time only a small experience has been reported, but this drug, or one similar to it, may provide, as well as a new approach, entirely new diuretic actions and, with them, clear advantages over the old diuretics

Trials with triazines have been reported from time to time, none of them very impressive as yet A recent one, amanozine, has been reported as superior to the others but this drug has not yet been subjected to sufficient clinical trial for a firm opinion

THE DESIGN FOR DIURESIS

Only therapy which takes into account (1) the nature of the fluid or electro
lyte to be removed, (2) the ease with which it can be done in the specific cas
with the agents available, (3) the need for speed in its removal, and (4) the se
ting in which it will be done (whether the home or the hospital where sodium i
take can realistically be controlled) will provide the greatest likelihood of succe
with diuretics

If edema is recognized in its least threatening stages, the measures for its re
will be the simplest, the disorders of water and salt balance incident to its remo
will be the most modest, and the success will be satisfactory without either dr
or discomfort If therapy is delayed until heroic measures are the only ones w
will provide sufficient relief in time, the nature of the necessary diuretic ac
ch that a degree of distress due to diuresis alone is inevitable, and, th

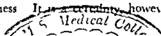
Specific toxic effects have not been described in detail in man although hypopotassemia, more easy to prevent than to control when established, is well recognized as a danger of chlorothiazide Skin rashes have also been reported and more recently it has been pointed out that, in the treatment of alcoholics with cirrhotic edema, there is a real danger of precipitating hepatic coma It is well to remember that the drug is related to the sulfonamides and there there is, therefore, a possibility of bone marrow depression and, at this early date, cases of agranulocytosis and thrombocytopenia have been reported The reduction of blood pressure in hypertension is an effect of chlorothiazide which has not been explained, but which may, if it induces precipitous depression of blood pressure, be a source of serious difficulty in some patients with heart disease Furthermore, there is the experience that this agent enhances the hypotensive actions of drugs commonly used in the treatment of hypertension In patients receiving such drugs for hypertension there appears to be a realistic danger in the careless use of chlorothiazide

Such a new and patently attractive drug may present the physician with a serious problem of choice Chlorothiazide appears to be a generally more desirable diuretic than acetazolamide (Diamox) It can be given for longer periods without the development of tolerance, while tolerance very quickly limits the utility of Diamox It is claimed that, unlike other diuretics, it is effective in patients using corticosteroids Unless the amino-uracils xanthines, and oral mercurials, it causes little gastric distress.

Chlorothiazide s negative features lie chiefly in what we do not yet know about it Like every effective drug it must have dangers, disadvantages and limitations These are not yet recounted in the literature on chlorothiazide, we have yet to discover them The extent to which it can replace or reduce the need for injections of mercurial diuretics in patients with advanced congestive failure and its effectiveness in stubborn edemas remain to be established We know nothing of the incidence of allergic or hypersensitivity reactions We know nothing of the effects of truly long term use (i e, usage comparable to the experience with mercurials for 10 or more years without ill effect) Already, however, the propensity of chlorothiazide to induce hypopotassemia is well recognized, and it is usual to attempt to control it, not always effectively though, with potassium chloride or orange juice Bone marrow depression and other blood dyscrasias have been reported This is not surprising in view of the close relationship to the sulfonamides In addition pancreatitis has been reported as a complication

Because of its apparent advantages I would choose chlorothiazide if I desired an oral diuretic I recommend that all who use it consider its undetermined limitations and dangers I advise that anyone unwilling to follow both the literature and the patient carefully use another oral diuretic It may be of interest that the manufacturers of Diuril are now purveying hydrochlorothiazide, which seems to have no practical advantage over chlorothiazide The tremendous success of

ment on their relative effectiveness It is a certainty, however, that there will be more of them



In choosing the proper diuretic it should be decided whether or not to use a parenteral mercurial diuretic rather than how long to try the others before succumbing to its unquestioned superiority In general, the oral diuretics are far more useful in maintenance therapy than for the initial treatment of the edema

Dosage —Dosage is better considered in terms of biologic effect than in absolute amounts Where time permits, a less than average dose, say 0 5 ml, of a mercurial diuretic can be used to test the patient's response to the drug In such a case, a dose can be adjusted which will induce an average diuresis of from 1 5 to 2 pounds A larger diuresis is likely to cause cramps or other symptoms due to transient electrolyte disturbance Where the time is short, the 2 ml dose may be used at the outset In some relatively resistant cases 3 ml of a mercurial may be a minimal effective dose In a few instances 2 ml has to be given twice a day before diuresis develops The latter dosages are rarely required and should be administered only after it is clear that the more than usual dosage is both essential and likely to be effective Whatever the diuretic used may be once the edema is satisfactorily relieved a dosage schedule should be established which maintains the patient in a state of normal hydration

RATIONAL BASIS FOR NEW DIURETICS

The potency of diuretics presently available is adequate for all common needs indeed, many of the fears about them are based on reactions due to the more than requisite response to some of these agents at the hands of the indiscriminating The qualities to be sought in new diuretics are listed here No available diuretic of adequate potency by the route generally recommended for its use possesses all of these qualities

1 Sustained rather than abrupt violent action
2 Reduced capacity for electrolyte upheaval
3 Convenience of administration, self administration (oral, rectal or subcutaneous)
4 Decreased toxicity (systemic and local irritant action especially of the gastrointestinal tract)
5 Effectiveness where others are ineffectual or contraindicated
6 Applicability in cases with a history of allergic reaction to other diuretics

In evaluating new diuretics, look for specific data on these issues and remember that early enthusiasms for new diuretics often are not supported by subsequent trials in man Such discrepancies may arise from the fact that the responses of many animals differ from those in man, in addition, clinical evaluation is determined in the patient with congestive heart failure, a condition which cannot be duplicated in the animal, and bio assay of diuretics in the patient with congestive heart failure usually provides answers which apply much more to potency than to long continued utility

SELECTED REFERENCES

Arnold, W P Medical Uses of Ion Exchange Resins, New England J Med 245 331, 1951
Bell, A L L, Smith, C N and Andreae E Effects of the Carbonic Anhydrase Inhibitor 6063 (Diamox) on Respiration and Electrolyte Metabolism of Patients With Re

small in comparison with the danger of the clinical condition, the danger of reac tion will increase

The aim of the design should be to bring about a normal state of interstitial hydration I deplore the use of the term 'dehydration" because it leads to implications of desiccation Tissues properly treated by diuretics are neither dry nor wet, they are normally hydrated The ideal therapeutic program is one which provides a daily salt and water balance, rather than the more commonly weekly or semimonthly salt-and water statement

Diet is a matter of the first importance Since patients with cardiac edema will probably sooner or later have to accept the salt poor diet, they would be well advised if they decided to do it sooner For those who have difficulty with the diet, the inevitable day can be deferred by the use of diuretics or doses more potent than would otherwise be necessary

Oral diuretics are desirable but, unfortunately they are often impotent for the purpose or irritant to the patient s stomach Oral diuretics are most likely to be of practical and continued utility in cases in which a modest diuretic action is satisfactory Such results are sometimes obtainable with small doses of Neohydrin If larger doses are necessary gastrointestinal distress is likely to arise sooner or later, at which time the problem of therapy will have to be faced and solved in a different way Because unpleasant effects are less common, Diamox is a useful diuretic Unfortunately, its effectiveness is brief and, although it returns after a waiting period, some other diuretic often has to be used between periods of Diamox therapy The xanthine diuretics cause gastrointestinal disturbances too frequently, even when used in suppository form, to be of value in any but the most unusual case Resins usually provide too many difficulties to justify their relatively small contribution to the relief of edema It may sometimes be possible to reduce the number of injections necessary by the supplemental use of oral diuretics, but, if the patient is not resistant to mercurial diuretics, this help is not required The most recent agent chlorothiazide (Diuril) seems to be the oral diuretic of choice

The mercurial diuretics are still by all odds the most effective and the most dependable diuretic agents we have today The undesirable results which have caused concern come from the fact that they are very effective rather than because of any defect Their use orally or rectally, as already indicated, has serious limitations No one organic mercurial diuretic is preferable in terms of effectiveness or decreased likelihood to induce electrolyte imbalance

Digitalis is indicated in virtually all cases of edema of heart disease In a large number, however, especially those with a normal sinus rhythm and those with an element of left sided heart failure, the benefits of the digitalis are not likely to be great enough to be easily discernible, while in many with advanced conges tive failure the mercurial diuretic clearly provides more relief than the digitalis used in the combination

Where cardiac patients, like diabetic patients, will inject a diuretic subcutaneously, frequent injections of relatively smaller doses of mercurial diuretics are both economical and feasible, and a frequent balancing of salt-and water intake and output may be achieved For such patients mercaptomerin or meralluride may be used

Chapter 6

THE CHOICE OF DRUGS FOR NUTRITIONAL DISORDERS

William B Bean, M D

INTRODUCTION

No animal can survive long when his diet consists of pure protein, fat, carbohydrate, and the necessary minerals. Man shares with many living creatures along the evolutionary scale the ability to live on plant foods or the tissues of other animals. These contain innumerable materials in addition to the three basic food constituents. Even a cursory view of the history of man's food and food habits shows there are no such things as good or bad tissues, or good or bad foods, or good or bad habits. Individual persons and whole nations have thrived on many different dietaries. Food customs provide a good illustration of Henning's dictum that there is nothing on earth which is not as much beloved by one group of people as it is detested by another. When given a wide variety of foods, man may not have always chosen the best diet, but he has managed to survive.

The medical puzzles introduced by the discovery of vitamins, their complex interrelationships, and the central position of food in human ecology highlight the difficult problem of nutrition. Dietary deficiencies have analogies with other dis eases where replacement therapy of an inherent deficiency is essential for surviva For example, certain lesions reduce or abolish the supply of hormones. The r sulting metabolic irregularities may be corrected by supplying extracted or sy thesized hormones, thus keeping the person not only alive but in good healt The use of insulin in diabetes and the use of steroid hormones in Addison's dise are examples. Dietary deficiencies are not inherent, but represent failures to bala supply and demand. Vitamins are used in therapy to pay back a debt. I *placement* rather than *replacement* therapy.

The appearance of clinical indications for employing vitamins and rel accessory food factors as drugs signifies that a serious breakdown has occurre the orderly processes leading to proper nutrition. There are many avenue which man may develop the clinical phenomena we recognize as pernicious an It may result from an inborn error leading to a functional disturbance as in sonian pernicious anemia. A basically similar disease may be produced by tapeworm harbored in the upper reaches of the small intestine. The tape

Bodansky, O , and Modell, W The Differential Excretion of Bromide and Chloride Ions and Its Role in Bromide Retention, J Pharmacol & Exper Therap 73 51, 1941
Brown, E A The Question of Reactions to Mercurial Diuretics, Ann Allergy 13 131, 1955
Council on Foods and Nutrition Nutritional Implications of Sodium Restriction, J A M A 149 1317, 1952
Danowski, T S Low Sodium Diets—Physiologic Adaptation and Clinical Usefulness, J A M A 168 1886, 1958
Dixon, L R , Kim, Y S , and Vander Veer, J B Clinical Experience With Chlorothiazide (Diuril), With Particular Emphasis on Untoward Responses, Am J M Sc 236 533, 1958
Dock, W , and Frank, N R Cation Exchangers Their Use and Hazards As Aids in Managing Edema, Am Heart J 40 638 1950
Fiese, M J , and Thayer, J M Value of Southey Leech Tubes in Rapid Relief of Massive Edema, Arch Int Med 85 132, 1950
Ford, R V , and Spurr, C L Electrolyte Excretion Patterns Due to Chlorothiazide, a New

Carbonic
t Failure,

J Med

Heidorn, G H , and Schemm, F
steroids in the Therapy
Hollister, J M , Lubash, G D ,
E H Refractory Ed
Mercurial Diuretics, Am
Iseri, L T , Boyle, A J , and Myers, G B Water and Electrolyte Balance During Recovery From Severe Congestive Failure on a 50 Milligram Sodium Diet, Am Heart J 40 706 1950
Johnson, D H , and Cornish, A L Acute Pancreatitis in Patients Receiving Chlorothiazide, J A M A 170 2054, 1959
Leiter, L Intractable Edema Clinical Therapeutic Implications, New York J Med 48 624 1948
Liddle, G W Aldosterone Antagonists, A M A Arch Int Med 102 998, 1958
Mackie, J E , Stormont, J M , Hollister, R M , and Davidson, C S Production of Hepatic Coma by Chlorothiazide and Its Prevention by Antibiotics, New England J Med 259 1151, 1958
Merrill, A J , and Wilson, J Continuous ACTH Therapy of the Nephrotic Syndrome, Am J Med 16 600, 1954
Minor, R W , editor Conference on Ion Exchange Resins in Medicine and Biological Re

Model , 1956
Model 39, 1959
Model talis and Mer
6 358, 1947
Moyer 0 2048, 1959
Pitts, Med 24 745,
1958
Pitts R F , Kruck, F , Lozano, R , Taylor, D W , Heidenreich, O P A , and Kessler, R H Studies on the Mechanism of Diuretic Action of Chlorothiazide, J Pharmacol & Exper Med 123 89, 1958
Pitts, R se of Diuretics,

Rubin, A e Management

Rubin, A in Congestive
lation 13 655,
1956
St

Sch

Sch
Sch

Vog
Zuc

upply system A man's entire need for vitamin K can be supplied by the action of enteric organisms if bile is available to promote its absorption

The nutritional needs of man are subject to adaptive changes so that a requirement may diminish under certain circumstances and may increase under others This is important in different parts of the world where the economic and educational status, climate, land, and customs provide peculiar diets for Arab and Eskimo, for Bushman and New Yorker Evolutionary forces may have led to the survival of certain groups fittest to thrive on particular and peculiar foods Influences of another kind are far more important in clinical medicine where organic diseases, neurosis, food fads, and even unwise therapeutic diets may provoke or precipitate actual deficiency diseases

The age of the biochemist, enzyme chemist, and animal nutrition expert is now with us The past saw much reluctance on the part of those in basic science to tackle the problems of clinical medicine Under the impact of laboratory research this has changed, and once the change came it continued with accelerating speed The trend of neglect has been reversed so completely that laboratory scientists have far outstripped the clinician in knowledge and understanding of many biologic and biochemical problems relating to nutrition Thus we are in the remarkable and uneasy situation of having a great many vitamins whose function in man is not known but is inferred by gross extrapolation from known or suspected biologic functions in lower organisms or from in vitro studies

There is vast perplexity in the clinical diagnosis and treatment of most vitamin deficiencies In a large population group, for instance inmates of a prison, eating the same poor diet several different deficiency diseases may develop many persons however will have no lesions or illness A sign usually attributed to a specific B vitamin deficiency may respond to the administration of another vitamin One vitamin may increase the absorption of another facilitate its metabolic function, or have a sparing action On the other hand if given in large amounts one vitamin may indeed increase the need for another It must be assumed that all tissues require all essential vitamins but one vitamin becomes a limiting factor in producing symptoms of disease or even death before another one equally deficient in the food causes perceptible trouble Since the B complex vitamins occur in natural foods together and since the potential pathologic response of tissues and organs is limited it is not surprising that several deficiencies produce similar lesions or that several different vitamins may produce clinical improvement of one lesion We do not yet understand many of these complexities

Before leaving the general problems of the need of various nutrients let us consider another element which makes the problem of daily requirements and hypothetically optimal levels of intake exasperatingly difficult In our laboratory w have measured specific vitamin content of several natural foods and of whole diet The vitamin and mineral content of an egg, a potato or a piece of steak may var greatly from that of an apparently identical specimen In spite of what nutritio tables tell us about the vitamin values of various foods the following factors a others need consideration when we try to estimate how much of a special vitan
ng into the tissues of our patients and ourselves For food plants alone
pecies variety, and genetic make up of the plant, (2) phys

gets the vitamin B_{12}, the host little or none Rarely, clinical vitamin B_{12} deficiency occurs when the diet has been very poor for a long time Alcoholism may be complicated by secondary deficiency diseases, though most cases of hyperchromic, macrocytic anemia in cirrhosis are not the result of B_{12} deficiency Finally, and not least important, diseases may produce secondary malnutrition in many ways Total gastrectomy, removing intrinsic factor, usually yields this kind of anemia if the patient survives long enough A blind pouch of bowel or a short circuit may result in a B_{12} deficiency, iron deficiency anemia, pellagra, or sometimes apparent good health These are the main kinds of processes by which the illnesses of undernutrition are produced Obesity, the opposite form of malnutrition, rarely requires drugs in therapy

There is hardly a field of clinical medicine where the questions of dosage, "requirement," and therapy have more uncertain answers than in nutrition While nutritional deficiency diseases and the many diseases which interfere with nutrition are the proper concern of the physician, clinical science has been relatively sterile in this field The serious perplexities, the long years of study, the inability to arrange short, neat, readily controlled tests, and the many reports of casual slipshod experiments masquerading as research have left clinical nutrition far behind other fields of scientific medicine This vacuum attracts the quack and the zealot who gull the ignorant from opposite motives

Living organisms require many contributions from their environment oxygen, constantly, sunlight and warmth, regularly, and then a host of minerals, energy materials, and preformed compounds which must be supplied to permit life to make its continual homeokinetic adjustments A clear rank order of the urgency of the several requirements exists Thus oxygen lack is fatal in minutes, deprivation of warmth is fatal in hours, of water in days, of calories and some minerals in weeks, of certain trace minerals, B complex vitamins, and ascorbic acid in months, and of fat-soluble vitamins and vitamin B_{12} in months or years

Barring an easy solution of the problem is the fact that not only do the needs of the organism vary with growth, age, size, activity, pregnancy, lactation, intercurrent disease and other influences but there are variations in time, secular trends, and a host of ecological relations scarcely investigated and little understood There are genetically determined variations in requirements which make each man different from every other man Of the approximately 60 different essential nutrients, any person may have some needs high, some low, and some moderate Requirements may be related to other factors, such as nonfat calories to thiamine One-way substitution may be possible, e g, tryptophan may serve as a precursor for niacin though the reverse exchange does not operate We do not know what determines the choice of metabolic pathways for tryptophan when niacin is in short supply Many complex organic compounds can be made by microorganisms living in peace and symbiosis in our enteric canals, though ruminants have a much better arrangement in their alimentary brewing vats Biosynthesis in the foregut of ruminants occurs where it is a real help since the products of fermentation must run the gauntlet of those parts of the gut where absorption is active In man biosynthesis in the cecum and colon are almost biologic afterthoughts although they may have some utility Vitamin K is an example of a completely self-sufficient do-it-yourself

may stalk latent beriberi Deficiency of the B complex vitamins which occur together in nature may produce signs and symptoms singly or in clusters Kaleidoscopic patterns emerge in a population group or even a family exposed to the same foods This may result from different actual intake or variable specific requirements or metabolic peculiarities—the geneotrophic individualities of Roger Williams Which are important or how they work, we do not know

Fat-Soluble Vitamins

The fat soluble vitamins of clinical concern are vitamins A, D, and K Vitamin E, long the cross eyed *stepchild, may* be admitted to a seat of *honor at the* table if its advocacy is taken from the hands of medical mythologists and restored to legitimacy Oral therapy with fat soluble vitamins is preferable unless sprue exists or bile is blocked or diverted from the gut

Vitamin A —Deficiency of the carotinoid vitamin A, said to be common in parts of the Orient, is very rare here The liver is tenacious of its stores Animals made deficient of vitamin A have defective vision, metaplasia and atrophy of epithelial tissues, and a disorder in the growth and remodeling of bones In man it has not been possible to separate the hypoplasia and increased keratinization of the *epidermis of vitamin A deficiency* from those of *starvation Affections* of the eye may progress from night blindness through dryness, thickening, and roughening of the lackluster bulbar conjunctivae, to *Bitot's spots, impaired* sensation in the cornea and sclera, reduced vision in good light, photophobia, edema opacification and ulceration of the cornea and the final ruin of panophthalmia

The treatment of vitamin A deficiency is to prescribe vitamin A This truism contains the essence of all vitamin therapy Fifty thousand to one hundred thousand units of pure vitamin A or potent extract of fish liver containing this amount should be given daily The sheet anchor of all vitamin therapy is to get the pa*tient over the hump with vitamins, restore his depleted stocks with concentrates,* and then provide and sustain an ample diet This is easy to say but may be hard or impossible to do Vitamin A deficiency develops slowly and responds with equal slowness so that therapy may have to continue for half a year or more *It is not* an emergency problem

Vitamin D —Vitamin D is the generic term for a group of related sterols which prevent or cure rickets When *there* is enough exposure to sunlight, a unique form of biosynthesis may occur in the skin if it is not too heavily *pigmented* The mechanisms by which vitamin D aids in the absorption of calcium *from the gut* and helps deposit *it as phosphate or carbon*ate in osteoid *and cartilage* matrix is a flagrant mystery But when vitamin D is inadequate, membranous bones and the shafts of long bones produce too *much uncalcified bone* Osteoid develops without lime salts, the soft rib cage *becomes* an inadequate bellows and the long bones warp and bow Cartilage cells without calcium salts fail to mature They accumulate and are distorted *Later degeneration* and efforts at repair by vascularization complete the sorry condition Only within limits can the fully developed process be reversed

In severe rickets 20,000 units of vitamin D are given by mouth each day Clinical and x-ray changes indicate *progress* After convalescence is established,

properties, mineral, organic, microbacterial elements of the soil on which it i grown, (3) sunlight, length of daylight, season of the year, as well as the growing time, (4) general climate and altitude, (5) ground moisture, rainfall, (6) the tim and method of harvesting and whether the plant is picked green or ripe, (7) th exact state of the food in collecting, transporting, and storing, (8) the processing refrigerating, drying, as well as bacterial contamination, oxidation, spoiling, (9 milling bleaching, mixing, homogenizing, chemical treatment and chemical pre servatives (10) methods of distribution, storage, packaging, exposure to heat moisture, light, and the duration of standing before ultimate sale (11) similar fac tors with reference to home storage, freezing, canning, (12) the preparation o the food including heating freezing thawing, drying cooking, standing after cook ing, disposal of cooking water (13) method of serving and, finally, (14) eating

The effect of variation of these factors is suspected and in a few cases meas ured, but for the most part it is unknown To such manifold variations in th vitamin or mineral content of standard items of food we must add the intricat and still not clearly understood processes of digestion absorption, and assimilation Perhaps the confusion may be epitomized by the unhappy thought that even th word "vitamin" is a misnomer

CLINICAL APPLICATIONS

A vitamin is an organic chemical compound, of simple structure (e g, niacin or complex structure (e g, cyanocobalamin) existing in natural plant or anima foodstuffs essential for the normal reproduction, growth, and metabolism of highe forms of animal life Unlike hormones which they much resemble the host is un able to synthesize them or at least enough of them for its requirements What i a vitamin for one species can be manufactured by another Ascorbic acid is a vita min for man and guinea pigs, but not for dogs or rats which may startle the cynic Water soluble vitamins whose function we suspect by data from laboratory obser vations are active in enzyme systems which govern energy transfers in the bus metabolic housekeeping which is coterminous with, or may be defined as, life Vita mins are active in very small amounts how small we now appreciate in the exampl of the vitamin B_{12} of which a day's supply is only about 1/60 billionth of the bod weight of the host

A vitamin, if a drug at all is not one in the ordinary sense though vitamin may have independent pharmacologic reactions and all can be poisons if give long enough at excessive levels Though vitamins have been used for an extrava gant array of ills and ails not related to a lowered stock in the tissues, their on undisputed use is to correct a deficiency If any genuine virtue resides in othe uses it will be winnowed out of our present vogue of therapeutic faddism which replacing an equally excessive therapeutic nihilism, has overreached itself

The proper use of vitamins is an individual problem In some instances ther is but a single deficiency and a single vitamin will correct it Scurvy responds t vitamin C In other situations the clinical signs may suggest that only one vitamin is seriously deficient but there may be gross dietary deficiencies of several factor causing humoral faults and upsetting some normal functions but not recognize by any sign as another specific vitamin deficiency syndrome With clinical pellagr

no certain connection as yet between any of the muscular dystrophies, hemorrhagic disorders, or disturbances of fertility and gestation in human beings and such signs of vitamin E deficiency in animals However, the negative aspects of Horwitt's studies where a vitamin E free diet has been given to many subjects for periods of many months should make us skeptical For the time being, vitamin E, though probably essential and perhaps very important has not been defined in terms of its role in clinical medicine

Water-Soluble Vitamins

Thiamine —Thiamine was called vitamin B_1 because it was the first element discovered in what was thought to be a single water-soluble vitamin It is the eldest of the numerous progeny, perhaps with more siblings to come Many reac tions are catalyzed by thiamine-containing enzymes, the majority having to do with the breakdown of pyruvic acid and alpha-ketoglutaric acid The biochemical and physiologic lesions of beriberi result from disturbances in carbohydrate metabolism Thiamine requirement is influenced by carbohydrate intake and total calorie ex penditure Deficiency of thiamine leads to beriberi Records from China suggest that it may have existed more than 2000 years B C Clinical beriberi may be a dry variety, peripheral neuropathy without cardiac complications or it may be wet beriberi with edema, cardiovascular symptoms, and peripheral neuropathy It has been suggested that peripheral neuritis may incapacitate a person and thus prevent exercise which might precipitate heart failure The mechanism by which a disturb ance in pyruvate metabolism produces a cardiovascular disorder is not known High cardiac output fast blood flow, wide-open arterial circuits, relaxed vasomotor tone, warm flushed skin pounding pulse, high pulse pressure, capillary pulsation and pistol shot sounds characterize wet beriberi It may end fatally with severe peripheral edema dyspnea and orthopnea Both the high output failure of wet beriberi and the peripheral neuropathy of thiamine deficiency have become ver rare in this country during the last ten years The improved economy of th country and the restoration to flour of some of the thiamine removed in the millin process probably account for this trend

Thiamine shares with other water soluble vitamins the tendency to be excret in the urine when it is given in large quantities For this reason, several doses 5 mg with meals and at bedtime are satisfactory except in critically ill patie where parenteral injection of 50 to 100 mg may be necessary even though much this will be lost in the urine If there is any doubt, employment of thiamine both methods is satisfactory As soon as convalescence is established, a good tritious diet together with supplementation of other B complex vitamins is n sary for proper therapy The neuropathy may fail to respond if the nerve c dead, but therapy for months with 5 mg daily may be associated with some m improvement

Riboflavin —The first demonstration of the relationship between biologi dations and vitamins followed rapidly after Warburg and Christian disc their flavoprotein enzyme This was followed shortly by the separation, ider nthesis of the prosthetic group It had long been known that h resembled pellagra but in which skin lesions w

3 teaspoonfuls of cod-liver oil a day may be substituted Sometimes refractory rickets occurs in older children and heroic doses up to one million units a day may be needed, but the hazard of a toxic reaction is great Of all the compounds having vitamin D activity, only D_2 (calciferol) and D_3 (activated 7-hydrocholesterol) have any real clinical application

Vitamin K —Deficiency of vitamin K does not occur in healthy persons, even on a diet devoid of the vitamin, because of biosynthesis in the alimentary tract Clinical difficulty with vitamin K deficiency develops when fat-soluble material cannot be absorbed This occurs notably in obstructive jaundice where bile does not reach the alimentary canal or in disease of the parenchymal cells of the liver where vitamin K is unable to play its part in the fabrication of prothrombin As a late stage in sprue or idiopathic steatorrhea, vitamin K deficiency may occur from failure of absorption At the present time, the commonest cause of the deficiency is the therapeutic employment of a direct antagonist of vitamin K, Dicumarol There is nothing specific about bleeding which occurs as a result of prothrombin deficiency induced by an inadequate supply of vitamin K The first thing that is noticed may be massive hemorrhage, or bleeding may begin insidiously with ecchymotic specks or most trivial purpura The use of wide spectrum antibiotics for a long period of time may eliminate bacteria which manufacture vitamin K, but clinical difficulty has been encountered only rarely in such circumstances Where vitamin K deficiency is caused by lack of bile in the alimentary canal, 2 mg of vitamin K orally with 1 or 2 Gm bile salts daily may prevent or correct the deficiency Vitamin K has been given prophylactically, 2 mg of menadione daily, in the last ten days of pregnancy in an attempt to avoid hemorrhagic diseases of the newborn, but evidence for its value is in dispute Phytonadione (Mephyton, K_1) is available as a 5 per cent aqueous emulsion in 1 per cent lecithin A 50 mg dose is administered intravenously over a period of 2 minutes If bleeding is less severe, two 5 mg tablets may be given orally Vitamin K is not effective against the hemorrhagic diathesis induced by heparin but only where Dicumarol has been given or the prothrombin time is low because of an inadequate supply of vitamin K

Vitamin E —Like most vitamins, vitamin E has been used enthusiastically but uncritically in a great variety of diseases for which there is no specific cure but for which there have been innumerable forms of treatment The evidence that it does any good in such circumstances is lacking The testimony is enormous No field of therapy is strewn with more wreckage of outmoded and futile effort than that of vitamin E Happily the recent flurry of using vitamin E for nonspecific ulcers and sundry kinds of heart failure has gone the way of puppy-dog fat and unicorn's horns

Actual vitamin E deficiency in man has been recognized only recently on the basis of the work of Gyorgy, Gordon Woodruff, and their associates Vitamin E deficiency has been sought in patients having difficulty with fat absorption, especially in patients with atresia of the bile ducts, or obstruction or fistulas, sprue, idiopathic steatorrhea, and cystic fibrosis of the pancreas A syndrome is beginning to emerge It is characterized by very poor absorption of vitamin A and other fats, low levels of serum cholesterol creatinuria, and decreased resistance to peroxide hemolysis All abnormalities are corrected by vitamin E therapy There is

nicotinic acid amide by mouth 3 times a day with meals is usually adequate, but doses 3 or 4 times this high may be given safely If patients are gravely ill and cannot eat, intravenous or intramuscular injections of 50 mg should be made at least 5 times a day, an effort being made to spread doses Supplementary vitamin tablets containing all the B complex vitamins should be given as soon as the patient can eat Additional concentrates include brewer's yeast up to 3 tablespoonfuls by mouth 4 times a day Supplementary feeding with eggnog and milk shakes is helpful Crude liver extract was used formerly but has no role now that purified preparations are available

Other materials can be used in the treatment of pellagra but they are of importance only in experimental demonstration Cozymase, the actual enzyme containing nicotinamide, may induce improvement in pellagrous glossitis in minutes Nicotinic acid amide and nicotinic acid take from many minutes up to a few hours Tryptophan is somewhat slower than nicotinic acid in producing its effects It usually takes 1 to 3 days before definite improvement occurs Improvement has followed ACTH, though the specificity of this response is most uncertain Diet and yeast take several days to several weeks to effect satisfactory therapeutic response Local therapy for the painful dermatitis, glossitis, and diarrhea is not necessary If the diarrhea fails to respond to ample quantities of nicotinic acid it is an indication that the patient is moribund and will respond to nothing

Pyridoxine (Vitamin B_6)—The only established role of pyridoxine in therapy so far occurs in infants The heat required to sterilize canned baby formulas destroys a large part of the pyridoxine in the milk Infants fed such formulas may develop irritability, colic, and convulsions This has been observed during the third month of life Most of the infants have appeared well nourished and well developed and have not had feeding problems

This disorder can be corrected by adding 2 mg pyridoxine a day to the baby's formula of a liquid diet In the acute condition, 5 mg of pyridoxine hydrochloride may be given intramuscularly at the beginning of difficulty and thereafter a supplement of 2 mg a day by mouth Now that the nature of this trouble is well recognized there should be no further difficulty since the deficiency in the formula is easy to correct

In spite of the demonstration that a clinical and metabolic disorder can be produced by a pyridoxine antagonist, pyridoxine has not proved useful in treating patients who have developed similar signs and symptoms while eating a normal diet

There is suggestive evidence that at times there may be an unusual requirement for pyridoxine during pregnancy Satisfactory balance studies have not been reported

Folic Acid—Partial solution of the folic acid mystery, while not disclosing all the secrets of the vitamin sphinx, is clarifying several problems A major biochemical function of pteroylglutamic acid is its enzyme action in fostering the synthesis of purines, pyrimidines, and certain amino acids by the incorporation of single carbon units Perhaps the only function of para aminobenzoic acid is in the synthesis of pteroylglutamic acid Under the influence of ascorbic acid free folic acid is converted into folinic acid, perhaps with the assistance of vitamin B_{12} Folinic acid acts in enzyme systems to liberate and transfer methyl and amino acid groups

sent Only after nicotinic acid became available could the situation be studied experimentally Sebrell and Butler made a series of classic observations on patients with induced riboflavin deficiency They developed angular stomatitis and greasy desquamation of the nasolabial folds The complete picture with angular stomatitis fissuring of the vermilion border of the lips crusting and desquamation of the mucous membranes magenta tongue and sometimes patchy redness and scaling on the scrotum have emerged The evidence is against an etiologic association of riboflavin deficiency and vascularization of the healthy cornea There is some variation in the rate of response to riboflavin but it is much slower than the response of clinical manifestations in beriberi or pellagra

It is preferable to give riboflavin in 2 to 5 mg tablets by mouth with meals More is retained when a 2 mg tablet is given after each meal than when a larger total is given in a single dose Vitamin supplements may be helpful but a well balanced diet is essential

Niacin and Pellagra —Nicotinic acid or closely related compounds are essential to the metabolic activity of all living cells The only known function is in the coenzymes containing nicotinic acid which catalyze almost fifty different chemical reactions One of the blights of contemporary investigation is the lack of any rational idea or any inspiration to gain a clue about how disordered chemical functions lead to the gross changes in function and structure which characterize the advanced states of malnutrition Most B complex vitamins function in enzyme systems transferring energy Whatever increases the requirements for oxidation therefore is likely to aggravate precipitate or hasten the advent of deficiency diseases But this tells us nothing of alternative metabolic pathways detour mechanisms for bypassing obstacles or finer homeokinetic adjustments which go on beyond our sight and understanding

Tryptophan and its role of treatment and prevention of pellagra illustrate the solution of a vexing puzzle which had plagued nutrition experts for some time The quantity of nicotinic acid in various diets did not have the expected reciprocal relationship to the risk of developing pellagra Sometimes pellagra was common in a population using a diet which contained more nicotinic acid than in another population using a diet with less nicotinic acid Among the possible reasons was a hypothetical toxic material requiring extra nicotinic acid to counteract it or a substitute which could pinch hit for nicotinic acid in the diet The observations of Krehl and his colleagues that tryptophan might be converted to nicotinic acid not only through biosynthesis of intestinal microorganisms but also in the body revived Goldberger s old and forgotten observation that tryptophan might be an important therapeutic agent in pellagra

Treatment —*In our experience in this country today*, it is uncommon for pellagra to result from a poor diet alone Usually there is some primary disease Therapy should follow two independent lines simultaneously A search for an underlying disease should be made If one is found which is correctible it should be treated appropriately Obstructive lesions along the alimentary canal require surgical correction or palliation Where metabolism is high efforts should be made to reduce it Alcoholism should be treated appropriately Specific therapy for pellagra should proceed as soon as the diagnosis is made For an adult, 100 mg

B_{12} facilitates the transfer of single carbon fragments, helps form nucleosides and nucleotides, and seems to have some role in the activation of S S groups On the other hand folic acid to be active must undergo metabolic conversion through folinic acid to a still incompletely defined active substance This reaction is facilitated by ascorbic acid but inhibited by aminopterin and other folic acid antagonists There is some evidence but not final proof that vitamin B_{12} may facilitate these reactions

Pernicious anemia, produced by a deficiency of vitamin B_{12} because of inadequate intrinsic factor, is treated with B_{12} parenterally Fish tapeworm anemia is caused by deficiency of vitamin B_{12} which results from absorption, utilization, or an inactivation of B_{12} by the tapeworm and perhaps by some inactivation of intrinsic factor In order to cause these reactions the worm must be fairly high in the alimentary canal If a vermifuge is successful in eliminating the worm spontaneous recovery develops slowly and is speeded up by parenteral or oral vitamin B_{12} Nutritional megaloblastic anemia is caused by a primary deficiency of vitamin B_{12} and a secondary deficiency of folic acid Treatment with folic acid or B_{12} is satisfactory The pernicious anemia of pregnancy results from a metabolic abnormality in enzymatic action of folic acid Large doses of folic acid correct the difficulty Refractory megaloblastic anemias are caused by a metabolic abnormality in the enzyme function of folinic acid and may be corrected by large doses of folic acid The megaloblastic anemia of sprue seems to come from a primary dietary deficiency of folic acid and a secondary deficiency of vitamin B_{12} Late in the disease organic lesions of the alimentary canal lead to deficiencies in many substances which are water soluble as well as fat soluble Megaloblastic anemias from blind pouches fistulas, and mechanical lesions of the alimentary canal usually result from an abnormality of folic acid metabolism associated with a deranged microflora of the gut They respond to folic acid surgical correction of the lesion or broad spectrum antibiotics

When vitamin B_{12} is needed several priming doses of 100 mcg should be injected A satisfactory maintenance program then is 50 mcg a month by parenteral injection There is no advantage in using expensive oral preparations with intrinsic factor

Biotin and Pantothenic Acid—Experimental efforts to produce biotin deficiency and one possible example of spontaneous biotin deficiency in a man addicted to raw eggs have been reported, but the problem remains in doubt We do not know the role of biotin in man or its function in metabolic economy and we are not sure of specific signs of a deficiency

Studies of the function of pantothenic acid in health and disease have been underway in our Metabolism Unit for more than 10 years There is much to suggest that pantothenic acid has many essential functions in human nutrition and metabolism among which seem to be an intimate role in the maintenance of potassium and perhaps other electrolytes, a suggestive function in the regulation of steroid hormones manufactured by the adrenal cortex, a possible role in maintenance of normal secretion of gastric juice and many suggestive functions in maintenance of carbohydrate metabolism It will take many years of painstaking studies to obtain conclusive evidence on these points

from simple compounds to help form purine and pyrimidine rings Under the influence of vitamin B_{12} the addition of pentose or pentose phosphate yields precursors for the nucleosides and nucleotides When methyl or formate is available, the process goes on to the formation of nucleic acid Decreased intake of pteroyl glutamic acid is rarely the single cause of deficiency though it seems to be a factor in the anemias of pregnancy and of sprue There may be inborn errors in enzymes required for its absorption though no disorder analogous to vitamin B_{12} deficiency or pernicious anemia is known In sprue, the pernicious anemia of pregnancy, and in megaloblastic anemias refractory to liver extract and vitamin B_{12}, folic acid in doses of 5 mg, 3 times a day with meals, ordinarily is effective In some cases the response will not be complete until vitamin B_{12} is added Rarely larger doses of folic acid will be needed

Vitamin B_{12} —Vitamin B_{12} has come to be accepted not only as the extrinsic factor of Castle but as the erythrocyte maturing factor of the liver Its relation to folic acid has not been resolved in all aspects In the normal person an enzymatic process occurs in the course of digestion which liberates vitamin B_{12} from its intimate binding with foodstuffs and facilitates its absorption In a person with *pernicious anemia, intrinsic factor is not made by the stomach in adequate amounts* Thus little or no vitamin B_{12} can be absorbed Since the liver can retain its supply for months, and occasionally even for years, signs of pernicious anemia may take a long time to develop Conversely, in a patient in whom pernicious anemia has been corrected by adequate doses of vitamin B_{12}, it may be months or years before a relapse occurs after maintenance with vitamin B_{12} has been discontinued Even after the blood has been restored to normal with vitamin B_{12}, the defect in the stomach and the histopathologic alteration of other cells still persists This can be demonstrated by Schilling's test for the absorption of radioactive vitamin B_{12} which is inadequate or absent in a person with pernicious anemia regardless of the state of the blood This is important in the separation of patients with posterolateral column disease into those who develop combined sclerosis because of inadequate B_{12} absorbing mechanisms and those who do not Since the neurologic manifestations of pernicious anemia may appear before any alteration in the blood, this test is helpful in discovering those who should respond to B_{12} and those who will not respond

Other mechanisms producing vitamin B_{12} deficiency include infestation with fish tapeworm, various enteric anastomoses, short cuts and blind loops of bowel, and protracted severe dietary deficiency of vitamin B_{12} and various B complex vitamins The clinical disease is the same It responds to adequate doses of vitamin B_{12} which may have to be given parenterally, or orally with intrinsic factor Probably all persons who have had a total gastrectomy may develop pernicious anemia Since such an operation usually is done for cancer of the stomach, there are relatively few who survive long enough for vitamin B_{12} deficiency to appear

If folic acid is given without vitamin B_{12}, therapeutically or by self-medication with vitamin pills, devastating manifestations of combined system disease may occur

When vitamin B_{12} is absorbed from the alimentary canal it does its metabolic work immediately without further change Its connection with folic acid, folinic acid, and ascorbic acid in hematopoiesis is not completely understood Vitamin

a 1 to 2 per cent solution in physiologic saline *In spite of its acidity it need not* be buffered or neutralized for intravenous injection Divided doses are advisable when it is given by mouth The emphasis should be on a generally nutritious diet and the correction of any intercurrent disease During convalescence 100 mg of ascorbic acid *with each meal and later 25 mg with meals* restore the depletion

In severely injured or burned patients, sometime in shock, and after extensive surgical operations, vitamin C may disappear from the plasma It is customary to give large doses to correct this laboratory finding, but there is little convincing evidence that the therapy helps, or the low level in the blood does specific harm Treating a laboratory datum is unsatisfactory therapy

GENERAL PHARMACOLOGIC CONSIDERATIONS

It is not surprising that vitamins and closely related chemical compounds have pharmacologic actions separate from their function as vitamins Vitamins are *poisons if used to excess The same is true of water, oxygen, or calories In our* shotgun approach to therapy, almost every disease with unknown cause or unsatis factory treatment has had a trial with vitamin therapy Even the enthusiasm of the naive investigator cannot identify any specific cures in what has been an unhappy chaos of credulity Vitamins are essential to life but their administration by unusual routes or in large quantities may be associated with anaphylactic shock, either mild, serious, or fatal Now that the blood level of tranquilizers is so often high the vitamin as placebo may be on the decline in autotherapy

Niacin

One of the great shocks which occurred in the early days of the employ ment of nicotinic acid in the treatment of pellagra was the discovery that it pro duced intense and sometimes unpleasant vasodilatation Since this had never been observed in experimental animals, it came as a complete surprise to those who tested *the compound on themselves before giving it* to persons with pellagra

Niacin administered orally or parenterally in sufficient doses produces a char acteristic train of symptoms Within less than a minute after intravenous adminis tration of 20 mg, a sensation of heat occurs in the skin It begins in the face and spreads over the chest, neck, and upper arms *Sometimes the entire body becomes* affected It may be particularly disagreeable in the perianal region The sensation of heat merges into a sensation of stinging and tingling of the skin Occasionally actual pain occurs At the same time there may be a sensation of fullness and throbbing in the head Extensive studies to identify the precise chemical structure of the compound responsible for producing this symptom were reported in 1939 It was found that only those molecules which contained the specific configuration *of 3 carboxy-pyridine had* the flushing and vasodilating property Thus sodium, ammonium, and ethylnicotinate, and nicotinic acid produced flushing It was not [illegible] 2 aminopyridine nicotinuric acid, nicotinic acid amide, or [illegible] e The observation that some of [illegible] to an early exploration of the use of vitamin antagonists in clinical nutrition, the preliminary details of which were

At the present time there is no known justification for the employment of pantothenic acid or biotin in human nutrition though inclusion of such materials in vitamin capsules for the treatment of severe undernutrition does not have any known contraindications

Ascorbic Acid —The slow working of the human intellect is illustrated in the long lag from the early clinical and folk knowledge of antiscorbutic foods and the circumstances under which scurvy might arise to the final isolation and synthesis of ascorbic acid Over 200 years ago James Lind summarized his medical experiences in the British Navy in his treatise on 'The Scurvy' He expounded its cause, described its cure illustrated its prevention and defined the disease and the treatment As an example of the ponderous movement of bureaucracy, the Lords of the British admiralty adopted Lind's recommendations as official doctrine for the Royal Navy after a lapse of only 40 years, but an even more ponderous delay occurred in the 125 years which were needed before students of chemistry and physiology finally came round to the isolation and synthesis of ascorbic acid

During the last two decades many of the obscure functions of ascorbic acid have been clarified in vitro but not the mechanism of its function in man In naturally occurring or induced ascorbic acid deficiency in man the first change is the keratinization of perifollicular papules After 3 or 4 months, erythema and finally bleeding into the hair follicles produces the classical punctate hemorrhage found chiefly in the lower extremities but sometimes over the entire body Bleeding then occurs subcutaneously, first with easy bruising then purpuric blotches involving large portions of the skin appear and finally very extensive hemorrhage occurs in and about joints, sometimes dissecting widely along fascial planes It may produce the same induration and swelling one sees in hemophilia although the ultimate contractures do not occur since the disease either responds to therapy or is fatal It is not a chronic disease In severe scurvy the gums become swollen, friable, and bleed easily on mild trauma, with hematomas, necrosis, infection, and sloughing The oral lesions are severe only when oral hygiene is poor They do not occur in an edentulous person afflicted with scurvy Wound healing is delayed

In infants and growing children, lesions of the bone produce characteristic subperiosteal hemorrhages and ultimately, deformity of the ribs In the wrists and ankles and at the end of other long bones a dense white line extends across the shaft as revealed in x ray examination It is caused by a deposition of calcium in the matrix Rarefaction of the adjoining bone emphasizes the abnormality Anemia may occur in children and adults who have scurvy The work of May and his associates has helped clarify the relationship of ascorbic acid and folinic acid in scurvy although the story is not yet completely told and we need more information in certain areas The pathologic physiology is a defect in connective tissue The teeth bone, and blood vessels are the major sites of characteristic lesions

With our present day emphasis on tomatoes and citrus fruits, and generally ample diet, scurvy is extremely rare in this country except in recluses who eat erratically according to whim and circumstance

When clinical scurvy occurs in an adult, it may be necessary to give as much as 2 Gm of ascorbic acid a day, preferably by mouth, although sometimes the mouth is so sore that swallowing is very difficult It may be given intravenously as

Hypervitaminosis D

Although intoxication with vitamin D occasionally occurs in therapy for rickets, particularly in refractory cases, most information about the effects of massive doses of vitamin D has accrued from patients given huge quantities of calciferol in the treatment of arthritis Relatively small doses have been fatal more commonly in children than in adults

The underlying pathologic effect is the precipitation of calcium in various tissues As a result of calcification in the kidneys, renal failure may occur with its characteristic train of symptoms Under certain circumstances the bones are demineralized apparently in order to supply the extravagant demands for calcium produced by such large amounts of vitamin D The histopathology is the same in young and old Calcinosis may affect literally any tissue or organ of the body—the joints with their synovial membranes the alveoli of the lung parathyroid glands heart muscle, the kidneys and the renal pelves, skin, lymph nodes, pancreas various arteries the lining wall of the stomach, and even the cornea and conjunctiva At first the bones may show accelerated calcification in the provisional zone of calcification Then comes thickening of periosteum Finally the cartilage itself is deformed Ultimately there may be demineralization of the bones

In contradistinction to the osteoporosis produced by parathormone, that produced by hypervitaminosis D does not lead to the replacement of the demineralized areas by fibrous tissue Based on experimental work, the initial renal lesion begins with actual deposition of calcium in the lining membrane in the cells of the distal tubules An inflammatory reaction follows, and later, obstruction with degeneration and ultimately failure of the nephron to function take place Inflammation which spreads rapidly throughout the kidney may increase the speed of destruction In addition to uremia occasionally hypertension and its attendant signs and symptoms have resulted

There is a dramatic variability in the amount of extra vitamin D required to produce intoxication It has been reported in one instance that 400 units a day have led to lesions which proved fatal In rare cases no more than 2 weeks of excessive therapy is necessary to produce discrete calcification The manifestations of hypervitaminosis D result from an enhancement of the usual action of the vitamin which increases the absorption of calcium from the alimentary canal and increases the urinary excretion of phosphorus In less severe cases the appetite is lost and nausea, vomiting and diarrhea may occur There may be weakness malaise occasionally polyuria headache various disturbances in cutaneous sensation patchy brown pigmentation of the skin and renal insufficiency

Nobody seems to have any good ideas as to the mechanism by which calcification takes place The best speculation is that damage to the cell occurs Then under certain unusual conditions of hydrogen ion concentration and perhaps actual mechanical interference with membrane function the abnormal deposit of calcium occurs But the physicochemical state required for this deposition is not understood In animals calcium may be deposited in spite of the fact that the serum calcium is normal or even low The role of the parathyroids is not clear It is unusual for any additional difficulty to be caused by exposure to sunlight or by large amounts of dietary calcium Other factors, however, such as the susceptibility of the indi

published in a review of 1944 The method has promise in studying vitamin function in man

Pharmacologic and Pathologic Actions of Vitamin A

Carotenemia —Carotene is an example of a vitamin precursor more complex than the vitamin, vitamin A being carotene divided in half Carotenemia is a state of increased carotene in the blood The condition is common when very high levels of carotene exist in the diet It may occur in young children eating an overabundance of carrots and related foods and occasionally in diabetics for reasons unknown

Carotene is one of the normal constituents of the human skin There is more in women than in men It is high in the skin of castrates and is reduced to normal levels after appropriate sex hormone therapy In carotenemia the skin may be discolored with a canary or sulfur color but the sclera are white and the mucous membranes are normal except for the palate which may be yellow The axillae, the palms, the soles, and the nasolabial folds are the most intensively discolored areas *in carotenemia*

Hypervitaminosis A —From ancient times Eskimos have known that polar bear liver eaten or fed to their dogs produced an acute prostrating illness which might end in death Kane, an Arctic explorer 110 years ago, described examples of severe illness occurring in semistarved Eskimos who feasted on polar bear liver Only in relatively recent times has it been recognized that the cause of the toxic effects of large amounts of polar bear liver were the enormous quantities of vitamin A it contained The vitamin A content of the polar bear liver is 18,000 units per gram If one managed to eat a pound of polar bear liver, he would receive in the neighborhood of 8,000,000 units It has been recognized for 30 years that excessive doses of vitamin A in experimental animals produce diarrhea, loss of appetite, unkempt fur, decalcification and spontaneous fracture of bones, scurvylike hemorrhages, and a variety of lesions in the internal organs The typical lesions result from an acceleration of the constant remodeling process which takes place during the maturation of bones In vitamin A toxicity more is resorbed than is laid down Periosteal new bone may be deposited along the shafts of the long bones where it should not occur at all While most cases of vitamin A intoxication have occurred in infants and children, it may also occur in adults Caffey has described the features of chronic vitamin A intoxication and presented some excellent photographs of the lesions

Occasionally an acute intoxication analogous to poisoning from eating polar bear liver may occur when a child swallows the entire contents of a 2 ounce bottle of vitamin A concentrate Headache hyperirritability, and sometimes a mild exfoliation of the skin occur In addition to Caffey's thorough review of toxicity in children, Shaw and Niccoli have reported hypervitaminosis A in a man His main complaints were hepatomegaly and a greasy, odorous skin, but he had bone and joint pain, alteration of the mucous membranes of the lips, weakness loss of weight and appetite Unless the disease is recognized and vitamin A intake is stopped, it may go on to death Usually it is recognized before this occurs This is a classical example of iatrogenic disease or suicidal or 'do-it yourself" disease

Table 5

Vitamin Group	*Common Name*	*Chemical Name and Properties*	*Biological Function*	*Clinical Deficiency Signs*	*Average Daily Allowance" for Normal Adult Per Kg Body Weight*	*Therapeutic Dose/Day*
Vitamin A	Vitamin A	3,7 dimethyl 9 (2',2',6-trimethylcyclohexen 1' yl) 2 4 6 8 nonatetraen 1-ol Solubility fat soluble Color and form pale crystals that melt into a thick, yellow oil Stability readily oxidizable but heat stable in air free containers	Unknown, appears to be needed for growth and integrity of certain epithelial tissues	Night blindness skin lesions metaplasia of epithelial tissues of respiratory tract, eye, and genitourinary tract	45 ± 5 mcg vitamin A or beta carotene	50 000 to 100 000 units of vitamin A
Vitamin B_1	Thiamine	2 methyl 5 (4 methyl 5 β hydroxethylthiazolium chloride) methyl 6 amino-pyrimidine hydrochlor de Heat stable white crystal freely soluble in water	The active form of thiamine is phosphorylated thiamine or cocarboxylase which is essential in decarboxylation of pyruvic acid with l beration of energy for muscle contraction	Dry beriberi, peripheral neuritis, peripheral neuropathy generally beginning in the feet, later in the hands with sensory changes first, motor changes subsequently, ultimately producing paralysis and contracture unless treatment intervenes Wet beri beri includes in addition to neuropathy, cardiovascular symptoms of high output failure and edema	20 ± 5 mcg	10 to 50 mg daily in divided doses parenterally or by mouth
Vitamin B_2	Ribo flavin	6,7-dimethyl 9 (D 1' ribityl) isoalloxazine Deteriorates in solution and on exposure to light but relatively stable to heat and oxygen Occurs as orange yellow crystals sparingly soluble in water	An essential constituent of flavoprotein coenzymes, in its phosphorylated form along with nicotinic acid enzymes is an element in the chain of reactions transporting hydrogen from metabolites to the blood stream to combine with oxygen	Angular stomatitis, cheilosis, glossitis, possibly seborrheic dermatitis, and scrotal skin lesions	25 ± 5 mcg	2 to 10 mg in divided doses orally or parenterally

vidual and the underlying disease for which vitamin D might have been given, as well as the age and the endocrine status of the patient all have an influence

In some persons with injured muscle a chronic pericardial lesion, or arteriosclerosis, calcium may be deposited Eventually, true bone may be formed Myositis ossificans seems to depend on an initial disturbance in tissue calcification although the mechanism here is not vitamin D intoxication

THE SEVERAL DRUGS

A description of the various vitamins is given in Table 5 together with additional information When using pure vitamins it is not known that one brand has an advantage over another as long as they meet the specifications of purity and strength required by law

Many concentrates and crude preparations are excellent sources of vitamins Thus fish liver oils are good sources of vitamin A There are other sources of vitamin D Whole brewer s yeast is an excellent source of protein and B complex vitamins, is relatively cheap and though unpalatable is an excellent supplement for those who have B complex deficiencies

Polyvitamin tablets and capsules vary considerably in the number of constituents they contain and in the concentration of different ones as well as in the number of minerals and sometimes the concentrates of vitamin rich material When these are to be used as supplements in the presence of severe malnutrition or actual vitamin deficiency diseases one should be careful to study the contents and not waste money on those with fancy labels and relatively small quantities of vitamins A careful study of the list of ingredients reveals that many things are put in for which there is no known function in human metabolism Some are almost certainly important others are not

Physicians are well advised to prescribe vitamin preparations manufactured by ethical pharmaceutical concerns since the actual ingredients of the tablet or capsule are likely to be reflected accurately in the label This is certainly not true of many preparations on the market which not only may contain much less but cost much more A physician should never prescribe just vitamins he should know the contents of various capsules and he should not be beguiled into believing that vitamins really correct old age pregnancy infections or any other trouble that comes along in spite of extensive advertising claims and innuendoes

A DESIGN FOR THE USE OF VITAMINS

The employment of vitamins as specific therapeutic agents is indicated when a clinically recognized deficiency syndrome exists It may have been produced by an intercurrent disease by a food fad or phobia or by the willful choice of an inadequate diet But for the most part it comes from socioeconomic breakdown in which the demand for food has outreached the supply because of poverty ignorance overpopulation war or famine There is no proper design for the use of drugs in therapy in nutrition The need for drugs means that prevention has failed Prevention—a good diet for everyone—would do away with the need for using any drugs at all We hardly hope to see the establishment of a utopian condition

Table 5—Cont'd

Vitamin Group	Common Name	Chemical Name and Properties	Biological Function	Clinical Deficiency Signs	Average Daily 'Allowance' for Normal Adult Per Kg Body Weight	Therapeutic Dose/Day
Vitamin B_{12}	Cyanocobalamin	$C_{63}H_{88}O_{14}N_{14}PCo$	Involved in stimulating the effect of folic acid on nuclear protein synthesis, metabolism, transmethylation, and conversion of carbohydrates to fat	Maturation arrest with hyperchromic macrocytic anemia and sometimes combined neurosis of spinal cord, probably has some role in peripheral nerve function	Probably less than 0 01 mcg	10 to 50 mcg / day and then maintenance 50 mcg / month parenterally
Vitamin C	Ascorbic acid	2,3-enediol L gulono-1,4-lactone	Somehow connected with the formation of connective tissue framework of the body and the protein matrix of osseous tissue and dentine, connected with metabolism of phenylalanine and tyrosine and integrity of the adrenal cortex, may have some role in biologic function of folic acid, its conversion to folinic acid, absorption of iron, and some still unknown function in cell metabolism and in respiration	Infantile scurvy with failure of growth and disorderly bone formation Adult scurvy with perifollicular hemorrhages, bleeding into joints, muscles, subcutaneous tissue, gingivitis, necrosis with infarction of mucous membrane of gums, general debility, inadequate wound healing	1 ± 0 25 mg	1 to 2 Gm by mouth or parenterally during acute stage, and 100 mg during convalescence
Vitamin D	Vitamin D	9,10 seco-5,7,10(10),22-cholestatetraen 3B-ol Soluble in fat solvents, sparingly in vegetable oils Fine colorless needles In proper ampules ergocalciferol is stable 6-12 months under refrigeration	Promotes absorption, retention, and balance of calcium and phosphorus perhaps by aiding in converting organic to inorganic phosphorus at site of lime salt precipitation in bone formations	Rickets with deformities of skull, ribs, pelvis, bowing of long bones, and in adults, osteomalacia with generalized rarefaction of bones, weakened bones with deformity and muscle weakness Occasionally hypocalcemic tetany	Adult requirement unknown	20,000 units vitamin D and in very severe cases up to 1,000 000 during acute stage
Vitamin K	Vitamin K	2 methyl-3-phytyl-1,4 naphthoquinone Fat soluble yellow oil stable to heat, air, and moisture, sensitive to light, alkali, and reducing agents	Stimulates synthesis of prothrombin in the liver but is not incorporated in the prothrombin molecule	Bleeding in association with low blood prothrombin	Adult requirement unknown	10 to 25 mg of menadione bisulfite parenterally

…n amide	Nicotinic acid	Pyridine 3 carboxylic acid amide Colorless crystals *Unusually stable to heat,* air, light, and alkali	In its phosphorylated forms as codehydrogenase I and II, *it is* concerned with hydrogen transport in same system as riboflavin	Nonspecific mental disorders, skin lesions, *disturbed* alimentary function glossitis	0 2 mg	50 to 500 mg / day orally or parenterally
Vitamin B_6	Pyridoxine	2 methyl 3 hydroxy 4,5 bis hydroxymethyl pyridine *White* crystalline plates stable to heat, acid and alkalies, destroyed by light	Concerned with protein metabolism and *fat metabolism* Codecarboxylase phosphorylated pyridoxal is concerned with removal of CO_2 from amino acids functions in transamination as *well as* conversion of tryptophan to niacin	In infants, growth impairment, convulsions and hyperchromic anemia Induced deficiency in adults gives rise to seborrheic dermatitis	25 ± 10 *mcg*	*Unknown*
Pantothenic acid	Pantothenic acid	D(+) N (2 4 dihydroxy 3 3 dimethylbutyryl) *β* alanine Pale yellow *oil* stable in neutral solutions but sensitive to heat, acids and bases	Presumably connected with acetylation in many systems *is* active in phosphorylated form probably as coenzyme A and has some influence on pyruvic acid oxidation is related to the integrity of *the* adrenal cortex and may be important in antibody formation	Unknown	Unknown	Unknown
Biotin	Biotin	Hexahydro-2 oxo 1 thieno [3 4] imidazole 4 valeric acid Long colorless needles Heat stable but readily oxidized somewhat unstable in presence of acid and alkali *benzoyl*	Unknown may be concerned with *transanimation* protein synthesis, and CO_2 fixation	Unknown	Unknown	Unknown
Folic acid	Folic acid	N [4 {[(2 amino-4 hydroxy 6 pteridyl)methyl] amino} benzoyl] glutamic acid Brilliant *yellow crystals* sparingly soluble in water Deteriorates on exposure to sunlight when stored at room temperature and when exposed *to heat in* acid medium	Concerned with nuclear protein metabolism probably by facilitating the formation *and* perhaps the utilization of thymine and other purines and pyrimidines May be required for the proper utilization of pantothenic acid and in association with vitamin B_{12} facilitates the synthesis of methyl groups	Maturation arrest with megaloblastic anemia and hyper*chromic* macrocytic red cells in peripheral smear classically seen in certain forms of malnutrition and in anemia the pernicious *anemia* of pregnancy	Unknown	10 to 20 mg / day in divided doses

reason, the modern paradox of a blind man searching in a dark room for a black hat which is not there We had better bear those *pills* we have than fly to others that we know not of

SELECTED REFERENCES

Bean, W B, Spies, T D, and Blankenhorn, M A Secondary Pellagra, Medicine 23 1-77, 1944 (see pp 57-58)

Bean, W B, Spies, T D, and Vilter, R W Asymmetric Cutaneous Lesions in Pellagra *Arch Dermat & Syph 49 335, 1944*

Bean, W B A Critique of Arm ... ored Medical Research Labor

Bean, W B, and Spies, T D ... lated Pyridine and Pyrazine C ... 20 62, 1940

Bean, W B, and Spies, T D Vitamin Deficiencies in Diarrheal States, J A M A 115 1078, 1940

Bean, W B, Johnson ... Henderson ... vey in Pacific

Bean W B Cc

Bean, W B, anc ... Clin Nutrition 1 267, 1953

Bean, W B, and Hodges, R E Pantothenic Acid Deficiency Induced in Human Subjects, *Proc Soc Exper Biol & Med 86 693, 1954*

Bean, W B Vitamania, Polypharmacy, and Witchcraft, A M A Arch Int Med 96 137, 1955

... r, F C The ... 175, 1954 ... 65 12, 1951 ... E L Cor ... of Methionine ... phthoquinone, Vitamin K S (II), J Clin Invest 37 70, 1958

Goldberger, J, and Tanner, W F Amino-Acid Deficiency Probably the Primary Etiological Factor in Pellagra, U S Pub Health Rep 37 462 1922

Gordon, H H, and de Metry, J P Hemolysis in Hydrogen Peroxide of Erythrocytes in Premature Infants Effect of Alpha Tocopherol, Proc Soc Exper Biol & Med 79 446, 1952

Horwitt, M K, Harvey, C C, Duncan, G D, and Wilson, W C Effects of Limited Tocopherol Intake in Man With Relationships to Erythrocyte Hemolysis and Lipid Oxidations, Am J Clin Nutrition 4 408 1956

Krehl, W A, Tepley, L J, Sarma, P S, and Elvenjem, C A Growth Retarding Effect of Corn in Nicotinic Acid Low Rations and Its Counteraction by Tryptophane, Science 101 489, 1945

May, C D, Sundberg, R D, Schaar, F, Lowe, C U, and Salmon, R J Experimental ... Relations of Ascorbic Acid and Pteroylglutamic ... in Animals, A M A Am J Dis

Rose, C ... ic Reaction in Vitamin E Deficient Erythrocytes, Am J Physiol 168 414 1952

Rothman, S Physiology and Biochemistry of the Skin, Chicago, 1954, University of Chicago Press

Sebrell, W H, and Butler, R E *Riboflavin Deficiency in Man A Preliminary Note*, U S Pub Health Rep 53 2282, 1938

Sebrell, W H, and Harris, R S The Vitamins, New York 1954, Academic Press, vols I, II and III

Shaw, E W, and Niccoli, J Z Hypervitaminosis A Report of a Case in an Adult Male, Ann Int Med 39 131, 1953

Von Bonsdorff, B Diphyllobothrium Latum and Pernicious Anemia, Mercators Trycheri, Helsingfors, 1948

Warburg O, and Christian, W Co fermentproblem, Biochem Ztschr 274 112, 1934

Woodruff C W Vitamin E Deficiency in Man Biochemical Evidence in a Patient With Xanthomatous Biliary Cirrhosis, Am J Clin *Nutrition 4 597, 1956*

in which each person in the entire population of the world would get a diet providing enough of each required factor too much of none. The precise intake would be highly individualized to suit measured needs No rational man believes that in society as we know it such a state of affairs will ever be possible Thus prevention at the earliest breach in the dike is a desideratum marvelous to contemplate but foolish to expect

Failing in prevention the next stage in the employment of vitamins as drugs would be to seek out persons whose diet is unbalanced whose calorie supply is adequate or more nearly adequate than the supply of vitamins particularly B complex vitamins Here if anywhere we need sensitive laboratory tests to detect specific vitamin deficiencies in the humoral stage before functional derangements become established, and long before the morphologic hallmark of a specific vitamin deficiency disease is apparent It is a commentary on the state of our ignorance or perhaps the unrealistic hope for such tests that we get very little aid from them *Neither tests of the excretion of vitamins in the urine nor tests of their level in the* blood nor the effect of a load test can give us the information we need about past dietary experience Tests reflect with fair accuracy the recent past of a given individual But a few good meals may disguise a long famine The notoriously uncertain history of eating experience and patterns is helpful within very narrow limits Thus we are a long way from being able to discover vitamin deficiencies in their incipient stages Even when we go back over the history of someone who has been studied carefully during the development of a deficiency we find signs and symptoms so nonspecific that they would not identify such persons in a large group The actual circumstances in which political economic and geographic factors conspire to produce malnutrition are such that the resources of society and medicine also are at a low ebb and cannot provide even the modest aids we have in early detection or delayed prevention

Another concern in our own present economic and geographic status is the question of the legitimate use of vitamins and vitamin mixtures in clinical practice today Lacking the absolutes we like to have as to indications for specific therapy, the answer depends upon our philosophy Should we accept the vitamin capsule or polytherapeutic tablet for a miscellany of nonspecific complaints in a throng of complaining patients? Should the public be encouraged or permitted to use at random or with compulsive regularity the ubiquitous vitamin capsule, following the do it yourself principle of self diagnosis and self treatment, naively hoping to avoid the usual unpleasant corollary of self medication namely self sacrifice? Partly to be doing something partly to remove the pressure and relieve himself of his guilty feelings of incompetence or impotence but mainly because of unhappy ignorance the physician may use vitamins by *default* *I don t know what to do* Vitamins won t hurt Let s try some vitamins The body reacts to large doses of vitamins as it does to poisons by eliminating them in the urine or by inactivation or by chemical decomposition We do not yet know whether large amounts of a single element of the B complex produces imbalances We do know that fat soluble vitamins A and D if taken too long in large doses produce serious and even fatal intoxication or chronic illness

Thus we are faced with a dilemma in the use of vitamins as drugs They are needed in high doses when a specific deficiency syndrome is diagnosed We are

takes to kill the bacterium), and the interfering or inhibiting effects of grease, pro teins, fluid, soap, and other substances that may be present

From a practical standpoint, the prime purpose of antiseptics is to prevent o limit infections Surgical technique can never be perfect so as to eliminate com pletely the entry of microorganisms into the body, even in "clean' operations For tunately, healthy tissues can take care of large numbers of bacteria without clinica signs of infection However, if the tissues are damaged or have a poor blood supply or if foreign material is also present, infection is apt to ensue Thus, another set of influential variable factors comes into play, complicating the "clinical evaluation' of antiseptics

Historically, the main factors affecting general acceptance or outmoding of antiseptics have been irrational ones--prejudice, convention, fashion, or sheer con venience The old lime and soda method of hand disinfection had much to com mend it, but it produced an unpleasant odor and so never became popular Bichlo ride of mercury hand soaks, once used almost universally, were gradually abandoned when other agents were introduced which did not darken the nails or roughen the skin Organic preparations of mercury and silver had their day, but were gradually discarded for reasons that are not entirely clear except that they became unfashion able The present vogue of hexachlorophene soaps and detergents for preoperative hand scrubs rests largely upon considerations of convenience and timesaving

Clearly, then, reliable evaluation of local antiseptics is a difficult task It can not be done precisely, it should not be done dogmatically The following attempt at assessment is based on a critical review of most of the extensive literature on the subject, ample clinical experience with each of the agents discussed and many years spent in testing them in the experimental laboratory

SKIN DISINFECTION

Nature of the Problem—It is not possible to sterilize skin without destroying it although it is possible to reduce the number of bacteria present The surgeon is compelled, therefore, always to operate with hands that cannot be fully dis infected, and to make incisions through skin that cannot be rendered entirely germ free It becomes a matter of prime importance to know which antiseptics are most effective

The skin is an irregularly pitted, ridged, and creased epidermal surface that normally is watertight and forms an effective barrier against bacterial invasion Bacteria are found in large numbers on the surface, on and under loosely attached flakes of keratin some microorganisms may be detected in hair pits and mouths of sebaceous ducts but few if any can be demonstrated in or between the living cells of normal skin

The cutaneous flora is composed of transient and resident bacteria Transients vary tremendously in number and kind Virulent germs as well as saprophytes may be present Most extraneous microorganisms that get on the skin soon dis appear from the surface or can be easily removed or killed Vast numbers can usually be found, however, under nails, between the toes, in the perineal breast and axillary folds, on the scalp, in the umbilicus, and on other areas that tend to [illegible] favor their multiplication Test

tate or roughen the skin, penetrate the epidermis so as to be absorbed systemically, or produce sensitivity Of secondary but practical importance are considerations of availability of the agent, economy in use, and the absence of unpleasant characteristics such as a disagreeable odor or permanent skin staining

Medical students often ask why, if rubber gloves are to be worn anyhow, it is necessary to disinfect the hands at all Unfortunately, many operators do not appear to know the answer themselves First, without preliminary hand preparation, it is almost impossible to "gown and glove" without serious breaks in aseptic technique Second, under rubber gloves, hands that have not been disinfected soon develop abnormally large bacterial populations Pathogens present participate fully in that increase A situation is thus created which permits dangerous spillage of bacteria through any tear or puncture hole in the glove Third, tears, puncture holes, and leaky patches in gloves occur more frequently than is generally recognized On my own service, where everyone was well alerted to these dangers, I found on occasion that as many as 20 per cent of the gloves used by the operating team had leaks in them by the time they were returned to the Central Surgical Supply Department Fourth, forearms of operators are not covered by impervious rubber but by a cloth sleeve through which underlying bacteria pass readily wherever and whenever the fabric becomes wet with sweat, saline, or blood

No way has been found to prevent an increase of the cutaneous bacterial flora under rubber gloves The best that can be done is to reduce the flora to relatively small size before putting on gloves, and then between operations to degerm the hands again by appropriate washing in alcohol or some other suitable antiseptic solution

Soap —Soap is a feeble antiseptic A cake of nonmedicated soap will sterilize itself quickly after use, but per se it is relatively ineffective in disinfecting the skin

Its great value lies in its detergent action, especially when washing is combined with mechanical friction Whenever the skin is rubbed or brushed with soap and warm water, grease, fats, dirt, and loose keratin come away, and with them most of the transient and a small portion of the resident bacterial flora

For preoperative scrubs, a preliminary toilet of the nails is recommended, followed by a 7 minute wash, using soap, a good nylon bristle brush, and running water, not neglecting any area between the finger tips and a level well above the elbows That procedure can be counted upon to remove all grease and dirt, all contaminating bacteria and about half of the resident flora Then the hands and arms should be dried with a sterile towel so that the following antiseptic solution will not be diluted and weakened by water left on the skin

Tests show that it makes little difference whether the detergent used is cake soap, liquid soap or tincture of green soap If the tap water used is very hard, a synthetic detergent may be preferable, but its degerming action will not be greater than that of ordinary soap used with soft water Medicated soaps (except those containing hexachlorophene) possess no advantage over nonmedicated, they are more expensive, and occasionally are found to be irritating Pure soap is rarely irritating to the skin if it is not used in a too concentrated liquid form

Hexachlorophene —Hexachlorophene is one of the few known antiseptics that do not lose their antibacterial potency in the presence of soap The combination

organisms (which are 'transients") placed on the hands are nearly all removed (above 98 per cent of them) by simple washing for a minute with soap under the tap, but to remove *all* of them with certainty requires 7 to 8 minutes of scrubbing with brush, soap and water

Residents form the stable bacterial population of the skin They live and multiply there Some of them die there, many are rubbed off or are washed off Under ordinary conditions of life increases tend to balance losses, so that on the same person the total number of resident microorganisms remains fairly constant Washing removes them slowly, and antiseptics are less effective against them than against transients In most persons the resident flora is composed largely of staphylococci of low pathogenicity, but some pathogens are almost always present also Prolonged or frequent exposure of the skin to large numbers of pathogenic bacteria may alter the ordinary composition of the resident flora and increase its potential infectiousness

Some persons habitually carry a much larger flora than do others, but it is not possible simply by looking at the skin to say whether its flora is large or small Some of the largest counts ever recorded have come from smooth, grossly clean, almost hairless skin of young women The rate at which the flora is reduced by scrubbing also varies with different individuals In general, the higher the initial flora, the slower the rate of reduction

In addition to the flora just described, there is a reservoir of bacteria hidden deeply in the skin The superficial resident flora comes off in washings at a regular rate, whereas the deep bacteria begin to appear in washings in appreciable numbers only after 15 or more minutes of scrubbing It is possible that many of these deep-lying bacteria come from sebaceous ducts

The distribution of bacteria on skin is found to be uneven, and contiguous areas may show different sized counts, but no constant or definite pattern has been discerned On the average exposed skin has a resident flora approximately equal to that of skin ordinarily covered by clothing The hands, arms, abdomen back, thighs and the dorsum of the feet all have counts of about the same size

After the cutaneous bacterial flora has been reduced by scrubbing or by antiseptics, regeneration occurs, probably following a growth curve similar to that seen in cultures Re establishment of the usual flora requires from one to several days, depending upon the thoroughness with which the skin has been degermed Under rubber gloves and impervious dressings, regeneration takes place much more rapidly

ANTISEPTICS USED TO DISINFECT THE HANDS

General Considerations—It is important in preparation for operation that the hands be scrubbed thoroughly so as to remove all dirt, grease, and natural fats, otherwise the antiseptic cannot make maximal contact with the cutaneous bacteria Tests have shown that about 7 minutes of conscientious scrubbing with brush, soap, and warm water are required, on the average, to eradicate virtually all fats from the hands and arms

Hand antiseptics should be both bacteriologically effective and harmless to the skin Since they may be applied several times a day to the same pair of hands and arms, they should not, even with prolonged and frequent use, injure or irri-

the stronger solutions, because it spreads evenly, wets efficiently
and because it is almost completely innocuous on the healthy sl
pens to contain some unusual, irritating, denaturing substance)

Solutions of alcohol exposed in an open basin for periods of
strength because the alcohol (95 per cent) fraction evaporates
does the water fraction

Timing is important also Washing the hands and arms v
70 per cent (by weight) alcohol has a degerming effect equivale
utes of scrubbing Washing for 3 minutes will be as effective, b
20 minutes of scrubbing If, in addition, one rubs the skin with
washcloth while washing in the alcohol the degerming rate will l

In the light of these considerations, the following routine is
a preoperative routine

Trim and clean the fingernails

Scrub under running water with nonmedicated soap (or soap, if desired) and a good brush, for 7 minutes (longer greasy and dirty)

Dry with a sterile towel

Rinse briefly in 95 per cent (commercial) alcohol to remo water (The small amount of this stronger alcohol solutio next basin will help maintain its strength)

Wash for 3 full minutes in 70 per cent (by weight) alcohol gently but thoroughly with gauze or a washcloth

Dry with a second sterile towel

Put on gown and gloves

This procedure is not unduly time consuming, is not hard o
can be relied upon to reduce the cutaneous bacterial flora far mor
any other simple routine known to the author

The same basin of alcohol may be used by a succession of op
day's end the used alcohol can be salvaged by filtering it and br
its original strength with the aid of an alcoholometer and approp

Isopropyl Alcohol—Isopropyl alcohol degerms the skin full
perhaps even a little better than, ethyl alcohol Solutions 70 per
or stronger are recommended In contradistinction to ethyl alco
cidal action increases with the concentration, so that full strength
somewhat more effective than 70 per cent

Since isopropyl alcohol is nonpotable, it may be obtained read
ated form, and without the annoying restrictions and taxes ordi
with ethyl alcohol However since isopropyl solutions are more
vents than equivalent ethyl alcohol solutions, they are more apt t
the skin if used frequently Repeated washing in isopropyl alc
hands rough and slightly scaly, with an uncomfortable feeling of

is a happy one Hexachlorophene itself is virtually insoluble in pure water, but the alkaline soap keeps it in solution Consequently, hexachlorophene combined with soap and other detergents has been recommended for surgical preparation of hands and the field of operation

Highly favorable reports have been published by Traub and co workers Udinski Seastone, and others Walter introduced a combination of a synthetic detergent with 3 per cent hexachlorophene, which, it is claimed, is even more effective than the soap preparations It has been asserted that persons who operate regularly need not scrub in the old fashioned manner, nor do they need to soak the hands in antiseptic solutions instead it is necessary only to lather the hands and arms for 2 or 3 minutes with hexachlorophene soap It has been alleged that washing with G 11 soap once a day will not only reduce the cutaneous bacterial flora to a very low level but will keep it persistently low

These glowing recommendations, together with the desire of many surgeons for a quick, easy method of preparing for operation, have resulted in wholesale adoption of hexachlorophene soap or pHisoHex in operating rooms all over the country, where they have tended to replace the conventional scrub and alcohol wash

It is only natural that the initial enthusiastic reports about hexachlorophene should have been followed by more critical re evaluations Several have been published These warnings are reinforced by a recent increase in incidence of infections in 'clean cases' in many hospitals In my opinion, the blame must be placed both upon overuse and undue reliance on antibiotics in surgical cases and upon the unreliability of the short hexachlorophene scrub

Hexachlorophene does not disinfect the skin quickly, as alcohol does, but only slowly over the course of several days This slow degerming action is attributed to a film of the agent left on the hands and arms after washing with the medicated soap It is possible to reduce the bacterial flora of the skin to about 5 per cent of its usual size, but to achieve this desired effect it is necessary to use G-11 soap exclusively and frequently (several times each day) for 4 to 5 days A single brief scrub with hexachlorophene soap or with pHisoHex is not significantly more effective than a scrub of equal length using ordinary soap

Furthermore, it has been demonstrated that at least some people have bacterial populations that are more resistant to this slow effect of hexachlorophene than others are Even in the case of those persons whose cutaneous bacterial flora has been shown by appropriate tests to be sensitive to hexachlorophene, it has been shown that an occasional wash with G 11 soap cannot be relied upon to keep the hands free from infectious germs, either under rubber gloves or in ordinary conditions of life

Ethyl Alcohol —Ethyl alcohol is probably the most effective and satisfactory hand disinfectant available

The concentration is important Strengths between 70 per cent by weight (approximately 80 per cent by volume when prepared at room temperature) and 92 per cent by weight (commercial alcohol, 95 per cent by volume) are all about equally effective against the bacterial flora of skin For routine use 70 per cent by weight is recommended because, volume for volume it is less expensive than

sore throat, may contribute an abnormally large number of pathogenic bacteria to the existing flora. Yet, the person preparing the field of operation is expected to disinfect the skin surface quickly and thoroughly—quickly because the surgical team is in a hurry and the crowded operating room schedule demands it, and thoroughly because the cutaneous surface is exposed during the operation and is not effectively sealed off, as hands are with rubber gloves.

However, the skin of the patient will usually tolerate stronger and harsher antiseptic solutions as a single application than is permissible on hands which must be disinfected repeatedly, day after day. Even so, one is limited, of course, to *antiseptics that do not harm the patient's skin*.

In using these stronger antiseptics, reaction time (between the chemical and the bacterial flora) cannot be ignored. There is no such thing as instantaneous disinfection by means of an antiseptic. Generally speaking, the longer the antiseptic has to act, the more effective it will be. However, the contact between bacteria and the bactericidal agent can be augmented and the rate of disinfection of skin can in consequence be increased by using gauze friction to apply the antiseptic. The spray method of applying antiseptic solutions is not recommended.

The old-fashioned custom of applying disinfectants to the operative site a day or two before surgery and wrapping the part in sterile dressings or sterile towels is bacteriologically useless and psychologically bad.

Soap.—The uses and limitations of soap as an adjunct in skin disinfection are discussed in the previous section on Antiseptics Used to Disinfect the Hands.

Soap is useful in preparation of the patient's skin for operation, but, generally speaking it does not have as large a role as in hand disinfection. Washing the field of operation in the operating room prior to surgery is sloppy, and may be dangerous if sterile drapes become wet as a result. It is better to wash the area ahead of time and have it reach the operating table grossly clean and dry.

Hexachlorophene.—The peculiar properties of this disinfecting agent have also been described in the foregoing section. A single wash with hexachlorophene soap or pHisoHex immediately before operation does not accomplish much bacteriologically. There is a place for hexachlorophene, however, in preparation of the field of elective operations especially in areas of the body not easily disinfected by ordinary means—such areas as hands, feet, face, and perineum. If those regions can be washed 3 or 4 times a day for 4 or 5 days prior to operation, they will come to surgery already pretty well disinfected. The instructed patient can carry out this this regimen himself at home. It is not necessary to keep the part wrapped during this preoperative period.

Ethyl and Isopropyl Alcohols.—Ethyl alcohol, 70 per cent by weight, and isopropyl alcohol, 70 per cent or stronger, are both superlative preparations for disinfection of the operative field, whether for major surgical procedures in the operating room or for minor office or ward procedures such as needle punctures. Seventy per cent ethyl alcohol is not a good fat solvent however, and should not be relied upon to do the work of a detergent. Full strength isopropyl alcohol is more effective from that standpoint.

The importance of the time factor must be kept in mind. Undue haste inevitably decreases the bactericidal effect of the antiseptic and increases the risk of subsequent infection.

A peculiarity of Zephiran is that its antiseptic action can be effectively neutralized by soap Even traces of soap regularly found on the skin of cleanly persons are sufficient to act as an antidote to Zephiran in aqueous solution Another characteristic of the compound is that extremely small amounts of it in culture media may inhibit growth of bacterial colonies to a degree that is thoroughly misleading to the unwary investigator

If Zephiran is to be used care should be taken to remove all soap from the skin first It is not sufficient just to rinse off visible suds with water Even thorough washing with water will not ensure elimination of all the soap clinging to the skin surface However, 40 to 70 per cent alcohol solutions are excellent, readily available soap solvents

Even when the epidermal surface has been rendered soap free by a preliminary wash with alcohol 1 1 000 aqueous Zephiran solution is a relatively weak skin antiseptic Tincture of Zephiran (1 1 000) is more effective though no better than plain 70 per cent alcohol which is much less expensive Indeed a considerable portion of the degerming effect of tincture of Zephiran is attributable to the activity of the alcohol acetone solvent

Zephiran in 1 1 000 solution is harmless on healthy skin except in extremely rare instances

It has become customary in some hospitals to prepare for operation by washing the hands with hexachlorophene soap and then washing in aqueous Zephiran solution before putting on gloves The poor logic of such a procedure should be obvious Many persons who follow that routine assume that the Zephiran will have an immediate antiseptic effect and will continue to depress the cutaneous bacterial flora during the period that gloves are being worn Such is not the case Not only is the antiseptic neutralized by the soap abundantly present on the skin under these circumstances but even when there is no soap present Zephiran will not prevent the multiplication of skin bacteria that seems always to take place under rubber gloves

Zephiran is one of a number of quaternary ammonium compounds They are all similar in skin antiseptic qualities Of those tested by the author (Phemerol Ceepryn and Diaparene Chloride) none has been found superior to Zephiran as a skin antiseptic

ANTISEPTICS USED TO DISINFECT THE FIELD OF OPERATION

Special Considerations—The problem of disinfecting the patient s skin for surgical procedures differs in several important respects from that of hand disinfection For one thing the patient s skin is not subjected to prolonged preliminary scrubbing as hands are *Although the patient s skin may appear grossly clean it* invariably harbors a large bacterial flora both transients and residents (including some pathogens) and this flora is protected to some extent by extraneous oils and natural fats when the antiseptic is applied In some instances this bacterial flora will be abnormally large That will happen if the ward prep (preliminary washing and shaving) has excoriated or scratched the surface That will also be the case if there is a nearby infection a draining sinus or a colostomy seeding the operative site with contaminating organisms Even a distant infection such as a

defect, however, of causing mild to serious burns on the skin of an unacceptably large proportion of patients even when care is taken to wash away with alcohol much of the mahogany colored coat as a final step before draping

The preparation formerly known as half strength tincture of iodine (pre 1947 tincture of iodine diluted with equal parts of 95 per cent alcohol) has about half the skin disinfectant power of the parent solution, but it is even more apt to produce burns, in my experience because the high alcoholic content evaporates rapidly leaving streaks and rims of highly concentrated iodine on the skin and it is at these areas under the drapes that painful burns are apt to occur

Modern iodine tincture which contains 2 per cent iodine, 2 4 per cent potassium iodide and 44 to 50 per cent alcohol, is a more satisfactory preparation than any of those mentioned above

Superior to all of them, however, in my opinion is a preparation of 2 per cent iodine in 70 per cent (by weight) alcohol This solution spreads evenly, dries slowly, does not burn the skin and rarely causes the patient discomfort of any sort Quantitative bacteriologic tests in my laboratory show this preparation of iodine to be more effective in reducing the cutaneous flora than any other antiseptic tested

These newer preparations of iodine deserve a larger place of usefulness in present day operating rooms

Povidone-Iodine—Povidone iodine (Betadine, Isodine), recently introduced as a topical antiseptic is a water soluble complex of polyvinylpyrrolidone and iodine which on contact with skin or mucous membranes tends to break down and release inorganic iodine slowly The slight residual stain on skin is readily washed away with water It is said that povidone iodine rarely irritates skin and that in the use of this preparation the toxicity of iodine is reduced For topical application a 10 per cent solution containing 1 per cent free iodine is available

In vitro tests against a variety of pathogenic organisms commonly found on skin and in wounds show that povidone iodine is effectively antimicrobial even in the presence of serum and blood The effectiveness and relative value of the agent as a skin antiseptic under conditions of actual use have yet to be demonstrated, however

Acrizane Chloride—This is the name given to a new antiseptic 9 parahexyl oxyphenol 9 chloro-10 methyl acridine It has been recommended in 1 200 and 1 1 000 concentrations in aqueous or alcohol acetone solutions Acrizane colors the skin intensely yellow and the stain may spread to dressings drapes and bed clothes For this reason *it may not be popular with hospital administrators* It is not irritating to skin

Tests show that both aqueous and alcoholic solutions even of the 1 1 000 concentration are highly effective skin antiseptics A limited trial on my surgical *service gave thoroughly* satisfactory clinical results

Chemical Detergents.—These substances have only slight skin antiseptic action *Even as adjuncts to skin disinfection* their usefulness is limited to the occasional necessity of removing adhesive tape marks heavy grease or oil paint tar etc

In the days of drop ether anesthesia a conventional step in preparation of the field of operation was to wash the area with an ether sponge The elimination of

Zephiran—The value and hazards of this agent are described in the fore going section on Antiseptics Used to Disinfect the Hands

Aqueous 1 1 000 Zephiran solution can be used safely around the eyes, but, because of its feeble antiseptic qualities, it is not recommended for skin disinfection elsewhere

Tinted tincture of Zephiran, 1 1,000 strength, is a relatively good skin antiseptic, however, if properly used The stain is not objectionable and enables the operator to make sure that no part of the operative field has been missed by the antiseptic

The following routine is preferred to all others on my own surgical service as the standard method of preparing the field of operation

Wash with alcohol
Wash with Zephiran
Wash with alcohol
Wash with Zephiran
Wash with alcohol

The alcohol used is either 70 per cent ethyl alcohol by weight, or 70 per cent iso propyl alcohol, the Zephiran, 1 1,000 stained tincture The alcohol not only re moves all soap which might interfere with action of the Zephiran, but it has powerful antiseptic activity of its own The Zephiran has, under these conditions, an antiseptic value about equal to that of the alcohol, and the stain ensures that there will be no skip areas The number of alterations forces the person applying the antiseptics to spend at least 3 to 5 minutes going through the routine, thus giving the germicides time to act This procedure does not harm even delicate skin, re duces the cutaneous flora very effectively, and does not appear to interfere in any way with subsequent healing of the incision

Iodine—Iodine has long been considered one of the best, if not the best, of all skin antiseptics from a purely bacteriologic standpoint, and rightly so The chief reason it has been largely displaced by other agents in preoperative skin prep aration is that it so often burned or irritated the patient s skin However, this was largely the fault of the preparations used It is only the occasional patient that is sensitive to topical application of iodine when applied in proper concentration

Iodine, in contradistinction to mercurials and some other chemicals, and alco hol fully reinforce each other's antiseptic activity on skin

Aqueous solutions of iodine should be used with some caution, especially the more concentrated preparations Lugol s solution (iodine 5, potassium iodide 10, distilled water q s ad 100), for example, may be dangerous if used on large areas of skin Three subjects in my laboratory, one after the other, who washed their hands and arms in the solution to test its antiseptic effects were all badly burned, and one of them had to be hospitalized for systemic symptoms of iodism However, Gershenfeld and others recommend a 2 per cent water solution of iodine iodide (iodine solution) and consider it a superior antiseptic

Strong iodine tincture, previous to 1947 called ' tincture of iodine,' contains 7 per cent iodine and 5 per cent potassium iodide in 83 to 88 per cent alcohol It is a powerfully effective skin antiseptic, even though it evaporates quickly and thus has a relatively brief time in which to exert its bactericidal action It has the

tions directly to wounds known to be infected with types of bacteria that are specifically sensitive to those agents That may be indicated especially in wounds and infections that are intractable to ordinary methods of treatment A good example is the treatment of certain stubborn infections with bacitracin This agent is not inhibited by pus, blood, or broken down tissue, or inactivated by penicillinase producers

SELECTED REFERENCES

Surface II Hexachlorophene

Lippincott Co

J Surg 94 938 1957

in New York Acad Sc 53 172, 1950

Klarmann, E G The Role of Antagonisms in Evaluation of Antiseptics, Ann N Y Acad Sc 53 123, 1950

Price, P B The Bacteriology of Normal Skin, a New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleansing J Infect Dis 63 301, 1938

Price, P B Re Evaluation of Ethyl Alcohol as a Germicide Arch Surg 60 492, 1950

Price, P B Benzalkonium Chloride (Zephiran Chloride) as a Skin Disinfectant, Arch Surg 61 23, 1950

Price, P B Fallacy of a Current Surgical Fad—the 3 Minute Scrub With Hexachlorophene Soap, Ann Surg 134 476, 1951

Price, P B, and Wilson, B L Acrizane Chloride, a Promising New Skin Antiseptic, Am Surgeon 19 792, 1953

Seastone, C V Observations on the Use of G 11 in the Surgical Scrub, Surg Gynec & Obst 84 355, 1947

Traub, E F, Newhall C A, and Fuller, J R Value of a New Compound (Dihydroxy ... Reduce the Bacterial Flora of Human

Udinski, Daily Use of a Soap Containing New Jersey 42 15 1945

Walter C York 1948, The Macmillan Co

that step was no loss from a bacteriologic standpoint Ether on a sponge is not even an efficient detergent for the skin

Acetone is an effective detergent and a fairly good antiseptic but it is somewhat injurious to skin

Carbon tetrachloride is a feeble antiseptic and is toxic as well

Chloroform and xylene have antiseptic actions comparable to that of alcohol but both substances are so irritating and harmful to skin that their use should be avoided if possible

THE USE OF ANTISEPTICS IN WOUNDS

Special Considerations —Closed wounds are usually uninfected wounds Indeed the most effective way to control and eliminate infection in an open wound is to convert it to a closed wound The habit of painting with an antiseptic the suture line of a freshly closed incision i a useless possibly harmful gesture

Open wounds are always infected to a greater or lesser degree The consideration of prime importance is not the presence of bacteria on the surface of the wound but rather the invasion of the body by those organisms Chronic wounds lined with granulation and fibrous tissue present a pretty effective barrier to bacterial penetration into underlying tissues on the other hand fresh wounds including burns in which there has not been time for the body to build up its defenses are subject to rapid and sometimes disastrous bacterial invasion It is in such situations that appropriate antibiotics given systemically may play an effective and decisive role

Local antiseptics have a very limited usefulness in wounds Mechanical measures such as the removal of all foreign bodies and necrotic tissue, free drainage and mild irrigations with physiologic salt solution avoidance of poor circulation and congestion and rest are generally much more important than topical drugs When antiseptics are used the chances are that they will be largely inactivated by serum blood pus necrotic tissue and dilution

Specific Local Antiseptics —Ether recommended half a century ago by Staige Davis appears to clean granulating surfaces well and is not painful to the patient but is of little bacteriologic significance

Dakin s solution (buffered aqueous solution of sodium hypochlorite) was introduced during World War I as an antiseptic irrigant for wounds It proved to be less effective in combatting infection and less innocuous to wounds than was originally thought It is no longer used to any extent neither is it recommeded

The application of caustics and strong chemical germicides to wounds is an old old story and in general a sad one Substances like alcohol iodine mercurials and silver nitrate do more harm than good

Some substances not strongly germicidal themselves have the effect of antiseptics because they can change the environment so that it becomes unsuitable for growth of specific organisms Examples are the application of oxidizing agents (hydrogen peroxide or activated zinc peroxide) for anaerobic infections, and more questionably the use of acetic acid solution for pyocyaneus infections

In selected cases it is rational and useful to apply selected antibiotic prepara

are useful and have clinical application because so many are histiotoxic The antibiotics which are clinically most useful are penicillin, streptomycin, tetracycline, oxytetracycline (Terramycin), chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), bacitracin, polymyxin B (Aeorosporin), neomycin, erythromycin, novobiocin, oleandomycin, and spiromycin [Griseofulvin is considered in the chapter on The Choice of Dermatologic Drugs Ed]

The bacterial spectrum and the sensitivity of various *microorganisms to the* different antibiotics varies enormously, but in general, antibiotics fall into patterns of activity that have been designated as narrow- or broad spectrum antibiotics Organisms have been designated as sensitive or insensitive Infections have been classified as being resistant or susceptible

There are four major antibiotics—penicillin, streptomycin, tetracycline, and chloramphenicol All of these antibiotics are widely used and, when they are properly selected and exhibited, *they are capable of controlling the majority of bacterial* infections In addition to these four major antibiotics, there are a number of minor antibiotics which are less active but nevertheless important therapeutic agents because when they are selected and used in patients with infections which are resistant to the major antibiotics or in patients who are hypersensitive to them, they are beneficial and often lifesaving They include those listed in Table 11

Mode of Action —It is now recognized that antibiotics like penicillin are bacteriostatic in low and bactericidal in higher concentrations, and that microorganisms are killed only when they are exposed to a high concentration of antibiotic during the active growth phase of multiplication While many very careful studies have been made to determine the mechanism of action of penicillin, the mode of *action has not been completely solved Several mechanisms have been suggested,* to wit, that penicillin prevents the entrance of some essential nutrient factor into the bacterial cell and probably blocks the retention of others already present It has been postulated that penicillin may be directly related to its ability to produce excessive dehydrogenation of sulfhydryl bearing compounds It is of the utmost importance that efforts be devoted to determining the mode of action of all antibiotics because to elucidate the mode of attack of a chemical molecule on a bacterium might lead to the design of a molecule that works as well or better and is far more effective and easier to make It has been postulated that the efficacy of all antibiotics is due to the molecule of the antibiotic being very but not quite like that of the normal and essential foodstuff of the bacterium so that when it is taken in it 'jams the works" and kills the organism

Selection of Antibiotics —One of the problems facing every doctor when he is confronted with a patient suffering from an infection is to establish a clinical and bacteriologic diagnosis He will want to know whether the infection is susceptible to any of the available antibiotics and, if so, which one he should choose There is a wide variety of agents to choose from, but the main object is to select the agent that will produce a positive effect in the shortest period of time

There are three broad classes of antibiotics in general use and a number with special and limited use The three common ones are penicillin, streptomycin, and the tetracyclines All of the others have a place, but the indications for their use are more limited They include those listed in Table 6

Chapter **8**

THE CHOICE OF AN ANTIBACTERIAL AGENT

Chester S Keefer, M D

INTRODUCTION

The development of new therapeutic weapons for the war against disease is clearly the most revolutionary factor in modern clinical practice It has altered profoundly the ways in which millions of people are treated when ill It has changed medicine and its practice in all of its aspects almost beyond recognition These revolutionary changes in medicine have created new possibilities for health and longevity which would have seemed fantastic even as recently as twenty five years ago This revolutionary force in medicine and especially in the field of antibacterial agents is now advancing with amazing swiftness so that we now make in years the advances whose past analogues required decades or even centuries

Physicians now have available a wide variety of highly potent and highly effective chemicals for the prevention and treatment of infectious disease New antibacterial agents are being discovered and applied Some have broad application others are limited The scene shifts from year to year as experience accumulates New problems are created and new methods of attacking them are required The choice of an antibacterial agent will depend upon many considerations but in general it can be said that one chooses an antibacterial agent that will bring the infection under control in the shortest period of time so as to save life and to shorten the course of the disease

For the treatment of most bacterial infections then there are a variety of anti infective agents These are often subdivided into the antibiotics the antituberculosis drugs and other chemotherapeutic agents such as the sulfonamides In this chapter a discussion of the choice of antibiotics and other antibacterial agents will be presented

ANTIBIOTICS

General Characteristics —The discovery, development and production of antibiotics for the treatment of infectious diseases constitutes one of the greatest advances of all time in medical therapeutics A wide variety of antimicrobial agents have been isolated from bacteria plants animal tissues, and fungi, but only a few

the site and nature of the infection The aim of treatment is to bring about recovery and control of infection in the shortest period of time and with the least inconvenience to the patient

ORAL PENICILLIN —A variety of dosage forms of penicillin are available for oral administration The sodium or potassium crystalline salts of penicillin G, penicillin combined with Benemid Bicillin and penicillin V are the common preparations The crystalline salts are combined with a buffer for the purpose of enhancing the stability and to increase the acid neutralizing capacity when exposed to the gastric juice Buffered preparations are not essential for a satisfactory therapeutic result

Penicillin combined with Benemid is used for the purpose of delaying the excretion of penicillin With this preparation it is possible to obtain plasma concentrations of the antibiotic which are comparable to those that are seen following the injections of the same amount parenterally Bicillin is absorbed more slowly than the crystalline salts and plasma concentrations of penicillin are detectable for a longer period of time

Penicillin V is another salt of penicillin which is given by mouth It is absorbed more slowly than crystalline penicillin G so that plasma concentrations reach their peak somewhat later and remain higher for a slightly longer period of time Biologically, penicillin V is no more effective than other forms of penicillin

More and more penicillin of all forms is being given by mouth It is well tolerated and it is as effective It is convenient and decreases nursing care and the discomfort arising from injections The incidence of serious hypersensitivity is lower The important point with oral preparations is the dosage schedule The therapeutic results following oral therapy are comparable in every way to parenteral therapy

While dosage schedules vary from one patient to another and from one disease to another when crystalline penicillin is used by mouth it is well that 3 to 5 times the minimum effective parenteral dose be used When penicillin is used with Benemid much less need be given because comparable plasma levels may be obtained with the same amount of penicillin as that given intramuscularly

PROCAINE PENICILLIN G —This is the most widely used parenteral dosage form of penicillin The preparation is relatively insoluble in water and is absorbed slowly from the site of injection Thus 1 or 2 injections daily will insure plasma concentrations of penicillin throughout the 24 hour period For example following the injection of 1 ml containing 300 000 units of procaine penicillin maximum plasma concentrations are reached within 1 to 2 hours The concentration then decreases slowly over a period of 24 hours Maximum plasma concentration following a single injection of aqueous crystalline penicillin G occurs within 10 to 15 minutes after injection and is always greater than that following a similar amount of procaine penicillin G but penicillin disappears from the blood more rapidly because the aqueous sodium penicillin G is absorbed more rapidly

Following the injection of 300 000 units of aqueous penicillin G, the plasma concentration is usually about the same at the end of 1 hour as at the end of 12 hours following the same dose of procaine penicillin

Sodium or potassium penicillin G is often combined with procaine penicillin [illegible] higher concentrations of penicillin as well as a 24 hour

Table 6 Antibiotics in General Use

Wide Use	Limited Use
Penicillin	Bacitracin
Streptomycin and Dihydrostreptomycin	Carbomycin
Tetracyclines	Cycloserine
Tetracycline	Chloramphenicol
Oxytetracycline	Erythromycin
Chlortetracycline	Fumagillin
N (Pyrrolidinomethyl) tetracycline	Kanamycin
Demethylchlortetracycline	Neomycin
	Novobiocin
	Nystatin
	Oleandomycin and Triacetyl oleandomycin
	Polymyxin B
	Ristocetin
	Spiromycin
	Vancomycin
	Viomycin

It is well, then to be familiar with the action and practical application of the various antibiotics so that the most effective one may be selected

Penicillin —Penicillin G continues to be the most widely used of all antibiotics It is the most potent and the least toxic It is available in a variety of dosage forms and it is bactericidal With the exception of an increasing number of strains of staphylococci practically all microorganisms which were originally sensitive to penicillin remain sensitive so that penicillin continues to be the antibiotic of choice for the treatment of all patients with gram positive coccal infections except the *Streptococcal faecalis* and the resistant staphylococci The one exception in so far as the patient is concerned is hypersensitivity to penicillin Further, it is the drug of choice for the treatment of gonorrhea and syphilis and of yaws (See Table 7)

Table 7 Diseases in Which Penicillin Is the Antibacterial Agent of Choice

All gram positive bacterial infections including
All sensitive strains of staphylococci
Pneumococcic infections
Hemolytic streptococcic
Nonhemolytic streptococcic
Anthrax
Actinomycosis
Tetanus
Diphtheria
Clostridial infections
Fusospirochetal diseases
Gonorrhea
Syphilis
Yaws

Dosage Forms —The commonest dosage forms are (1) crystalline penicillin G for oral use (2) sodium or potassium salts of penicillin G for injection in aqueous solution (3) procaine penicillin G suspended in water or aluminum stearate (4) crystalline penicillin combined with Benemid to delay excretion, (5) combinations of aqueous soluble and procaine penicillin and (6) penicillin V

The selection of a dosage form will depend upon the individual patient and

Table 8 Diseases in Which Streptomycin and Dihydrostreptomycin Are the Antibiotics of Choice

Tuberculosis—combined with isoniazid or P A S
Tularemia
All gram negative bacterial infect ons due to sens t ve stra ns
H influenzae—combined with sulfadiazine
K pneumoniae—combined with sulfadiaz ne
Granuloma inguinale
Plague—combined with sulfadiazine

used for the treatment of *H influenzae* meningitis it is well to combine its use with sulfadiazine in order to delay the emergence of resistant strains *Klebsiella pneumoniae* infections and mixed infections of the peritoneum are also treated with streptomycin The dosage and duration of treatment should be guided by the clinical response and the severity of the infection Optimum therapy should be employed for 7 to 14 days or before resistant organisms emerge

CONCENTRATION AND DOSAGE —Following intramuscular injection streptomycin diffuses freely into the blood stream and lymphatics and can be detected in the peritoneal and pleural fluid, the aqueous humor, and the bile It diffuses into soft tissues and into abscesses

Streptomycin is excreted in the urine and in the bile At least 60 to 80 per cent of the streptomycin injected may be recovered in the urine within 24 hours

For intrathecal injection a single injection of 25 to 50 mg every 24 hours is usually adequate

Streptomycin may be used locally by inhalation in solution in infections of the ear or the conjunctivae or in the pleural or peritoneal cavity

The reactions to streptomycin are discussed under Side Reactions to Antibacterial Agents

In short streptomycin and dihydrostreptomycin are the antibiotics of choice in the treatment of tuberculosis tularemia and gram negative bacillary infections sensitive to the antibiotic Other infections listed in Table 8 also respond

The Tetracyclines Tetracycline, Oxytetracycline Chlortetracycline—These three antibiotics can be considered together because tetracycline is essentially the *basic chemical structure for oxytetracycline and for chlortetracycline* All three are equal in their biologic activity all three are useful in the same infections and cross resistance of organisms is common The incidence of side reactions may differ from one agent to another but nausea vomiting and diarrhea may be observed with any one of them

Tetracycline diffuses into the cerebrospinal fluid in greater amounts than the other two but it has no demonstrable effects on the central nervous system in that it is not antispasmodic or anticonvulsant and it is not a sedative

The tetracyclines are classified as broad spectrum antibiotics because of their *range of activity They are bacteriostatic* in their action and do not kill microorganisms directly unless the ratio of the concentration of antibiotic to the initial number of bacterial cells is very high All three agents are more histiotoxic than penicillin or streptomycin These agents when used alone or in combination with other agents are highly effective and play a most important role in supplementing penicillin and streptomycin in the war against infections

concentration in the plasma The combination is usually 100 000 units of the crystalline salt and 300 000 units of procaine penicillin per milliliter

PROCAINE PENICILLIN IN ALUMINUM MONOSTEARATE —Procaine penicillin G suspended in oil and aluminum monostearate is absorbed more slowly and uniformly than procaine penicillin G alone When this preparation is used the maximum penicillin levels are lower than when other preparations are injected but the plasma concentrations persist for a longer period of time The usual amount injected is 300 000 to 600 000 units or more and under these circumstances penicillin may be found in the plasma for 3 to 5 days

AQUEOUS SOLUBLE PENICILLIN —The sodium and potassium salts of penicillin G for injection in aqueous solution are used widely in all acute infections susceptible to its action They are absorbed rapidly so that maximum plasma concentrations develop within 15 to 30 minutes after injection and then depending upon the dosage employed disappear within a period of 3 to 6 hours

Aqueous soluble penicillin can be given intramuscularly intravenously intrathecally or into the serous cavities, depending upon the need and the site of infection Dosage schedules are planned so that the maximum therapeutic effect is obtained in the shortest period of time

The dosage schedules have varied widely and often 300 000 to 500 000 units or more of aqueous penicillin are injected every 3 to 6 hours, depending upon the severity of the infection

Penicillin G is often used as an inhalant in chronic pulmonary infections and it is incorporated into troches for its local effect in the mouth and throat Finally it is combined with various ointment bases for local application to the skin or conjunctivae

In short a wide variety of dosage forms of penicillin are available for selection and application The reactions to penicillin vary with individuals and with previous experience with the agent These are discussed under Side Reactions to Antibacterial Agents

Streptomycin and Dihydrostreptomycin —Streptomycin and dihydrostreptomycin are used most widely for the treatment of tuberculosis Usually they are combined in equal amounts in order to reduce the incidence of neurotoxicity of the eighth cranial nerve and as a rule they are administered with isonicotinic acid hydrazide and/or para aminosalicylic acid in order to delay the emergence of resistant strains of tubercle bacilli

MODES OF ADMINISTRATION —These antibiotics are administered intramuscularly topically and orally The oral route is used only when a local effect in the intestinal flora is desired but this route is not used for the treatment of systemic infections because very little is absorbed from the gastrointestinal tract For all systemic infections in which these antibiotics are used the intramuscular route is employed For the management of meningitis, both the intramuscular and intrathecal route are employed In empyema direct injection into the pleural cavity is desirable

CLINICAL INDICATIONS —Streptomycin or dihydrostreptomycin is the antibiotic of choice in the treatment of tuberculosis tularemia *Hemophilus influenzae* infections —especially meningitis urinary tract infections due to gram negative bacilli and all forms of bacterial meningitis due to gram negative microorganisms When it is

good evidence that chloramphenicol diffuses into the tissues and is excreted in the bile and the urine Small amounts appear in the cerebrospinal fluid Most of the drug administered by mouth is recovered from the urine within 24 hours although most of it is in an inactive form of the drug Enough of the active drug appears in the urine, however, to render it bacteriostatic to susceptible organisms

Chloramphenicol is active against gram positive as well as gram negative organisms but its main effect is upon gram negative bacteria It resembles streptomycin in its bacterial spectrum but it is very much less active against the tubercle bacillus The action against the typhoid bacillus and the rickettsial organisms is striking Some activity is present against psittacosis, lymphogranuloma venereum and Newcastle virus when its potency is tested in vitro

Clinical Uses —Chloramphenicol has been highly effective in the management of a variety of medical and surgical infections due to staphylococci The most striking results have been observed in the treatment of typhoid fever, the rickettsial diseases brucellosis urinary tract infections and penicillin resistant staphylococcic infections Also, favorable results have been observed in some cases of primary atypical pneumonia and *H influenzae* infections (Table 10)

Table 10 Diseases in Which Chloramphenicol Is the Drug of Choice

Toxicity —In general it can be said that chloramphenicol is well tolerated and produces few side effects Hypersensitivity of the serum sickness type has not been reported Abdominal cramps vasomotor reactions such as coolness of the skin and weakness of the legs have been recorded

The most undesirable side effect of chloramphenicol has been the development of some form of blood dyscrasia in a few patients Leukopenia agranulocytosis thrombopenic purpura, and aplastic anemia have been reported Protracted treatment and repeated courses of treatment are predisposing factors

However, blood disorders have been reported after a few days of treatment in occasional patients One of the rules of administration should be that the patient is followed closely and the blood should be examined repeatedly for any significant change Discontinuing treatment at the first sign of leukopenia is usually followed by recovery

Bacitracin —This antibiotic is derived from a strain of *Bacillus subtilis* It is a polypeptide and has the same general bacterial spectrum as penicillin It can be administered locally or parenterally and it is used in cases of penicillin insensitive infections, especially staphylococcic infections of wounds of the meninges and of the endocardium It is most frequently used topically in various forms of ointment It is soluble in water or physiologic salt solution and when given intramuscularly it is dissolved in 2 per cent procaine solution in physiologic saline in order to decrease the local pain at the site of injection

Table 9 Diseases in Which the Tetracyclines Are the Antibacterial Agents of Choice

All mixed bacterial infections due to susceptible organisms
Wound infections
Respiratory infections
Peritonitis
due to sensitive organisms
Rickettsial diseases psittacosis and lymphogranuloma venereum
Primary atypical pneumonia
Brucellosis

Mode of Administration —The tetracyclines are usually given by mouth They are absorbed from the gastrointestinal tract, and the plasma concentrations reach their peak within 2 to 4 hours When 1 Gm is given at intervals of every 4 to 6 hours, the plasma concentrations remain within a predictable range of 5 to 20 mcg per milliliter of plasma

They are excreted in the urine and after a single dose they may be detected in the urine from 1 to 24 hours later

Solutions are available for intravenous administration or for topical application

Clinical Uses —These agents have very wide use and application in a wide variety of bacterial and rickettsial diseases They are used in all cases of bacterial infection when a patient is sensitive to penicillin or when the organisms are resistant to other antibiotics They are also used widely and extensively as a temporary cover for the treatment of infections until the bacteriologic diagnosis can be established or when it is impossible to establish such a diagnosis

As a rule, then the most logical use of the broad spectrum antibiotics is in the treatment of gram negative bacillary infections and the rickettsial diseases and of all gram positive infections resistant to penicillin and in the treatment of all patients with sensitive bacterial infections who are hypersensitive to other antibiotics The diseases in which the tetracyclines are most useful are listed in Table 9 and the side reactions are discussed in the section devoted to reactions

[Two new forms of tetracycline N (pyrrolidinomethyl) tetracycline (Syntetrin) which is said to be 2 500 times as soluble as the older forms and demethylchlortetracycline (Declomycin) have just been introduced Although they may well have special merits there has been insufficient experience with them for an opinion at this time Ed]

Chloramphenicol (Chloromycetin) —This antibiotic is produced by either chemical synthesis or fermentation Originally it was derived from fermentation using *Streptomyces* as the mold It contains a nitro group and a dichloracetic acid residue with nonionic chloride It was the first broad spectrum antibiotic to be isolated as well as to be synthesized

Mode of Administration —Chloramphenicol is a crystalline agent which is usually given by mouth It is absorbed rapidly from the enteric tract, and the maximum plasma concentration following a single dose is reached within 2 hours It gradually decreases over a period of 8 hours and none of the drug is found after 24 hours Plasma concentrations are related to dosage and to time There is

the agent must be discontinued if the injury is appreciable In many cases the drug has been lifesaving and renal injury has been minimal or absent

Cycloserine (Seromycin) —This antibiotic has been used most widely for the treatment of tuberculosis although it has had therapeutic trials in other infections as well When it is employed in tuberculosis it is generally combined with isoniazid Both agents are active and useful in treatment of streptomycin resistant tuberculosis Cycloserine has very little therapeutic effect or application in other bacterial infections and its use should be reserved for patients with tuberculosis resistant to streptomycin and other antituberculostatic drugs

Carbomycin (Magnamycin) —This antibiotic is produced from *Streptomyces halstedii* It consists of two biologically active components which are equally effective against microorganisms but have somewhat different pharmacologic properties in that one component is absorbed from the gastrointestinal tract more rapidly than the other Carbomycin also has been isolated from a strain of *Streptomyces hydroscopicus*

Bacterial Spectrum —Carbomycin is a narrow spectrum antibiotic with a bacterial spectrum resembling erythromycin that is it is most active against gram positive organisms but demonstrates little activity against gram negative organisms It has some activity against rickettsiae and psittacosis Organisms become resistant to it slowly and in the fashion of penicillin resistance There is no cross resistance with other antibiotics except erythromycin Erythromycin is more active and more potent than carbomycin but there is cross resistance between the two They have similar empirical chemical formulae and similar absorption and excretion patterns

Inasmuch as carbomycin and erythromycin are identical in most respects although they are not chemically the same the one may be used for the same indications as the other (See Erythromycin)

Erythromycin —This is an antibiotic elaborated from *Streptomyces erythreus* and it is produced in crystalline form from its basic compound It is relatively insoluble in water (2 mg per milliliter) but highly soluble in alcohol and in organic solvents

Erythromycin is active in a slightly alkaline medium and is not affected by substances which are known to inhibit penicillin streptomycin or the sulfonamides It has a moderately broad spectrum of activity but gram positive organisms including *Staphylococcus aureus* are highly sensitive to erythromycin Group A hemolytic streptococci and pneumococci are most sensitive and *Escherichia coli* Proteus and Pseudomonas are all quite resistant

Mode of Administration —The usual mode of administration is by mouth since it is readily absorbed from the intestinal tract The plasma concentration can be correlated with the dosage, and peak concentrations are reached within 1 to 2 hours after each dose and decline rapidly so that the agent is no longer detected after 4 to 6 hours Only small amounts are formed in the urine The usual dosage is 250 to 500 mg every 6 hours

Clinical Use —Erythromycin is most valuable in the treatment of diseases due to penicillin resistant *Staphylococcus aureus* infections and in the management of pneumococcic and hemolytic streptococcic infections in people who are hypersensitive to penicillin It is not the drug of choice for the treatment of these in

Bacitracin is absorbed very slowly from the gastrointestinal tract so that very little reaches the tissues when it is given by this route Intestinal bacteria including Clostridia and gram-positive organisms such as staphylococci and enterococci are inhibited in their growth when it is given by mouth

Following intramuscular injection, this antibiotic appears in the blood and tissues but very little diffuses into the cerebrospinal fluid It is excreted slowly, mainly by the kidneys, but, in contrast to penicillin, the plasma concentrations may continue elevated for several hours following a single injection

Table 11 Uses of Narrow Spectrum Antibiotics

Bacitracin	Used locally for treatment of wounds and superficial infections of the skin and to reduce bacterial flora of gastrointestinal tract Used systemically for treatment of resistant staphylococcic infections Incidence of hypersensitivity is low and bacterial resistance develops very slowly
Erythromycin	[illegible]
Neomycin	[illegible] reduce the bacterial flora of the gastrointestinal tract Used systemically in treatment of staphylococcic infections resistant to other antibiotics [illegible]
Polymyxin B	[illegible] iosa [illegible]
Oleandomycin	[illegible]
Triacetyloleandc	[illegible] in [illegible]
Novobiocin	[illegible] Also Pro [illegible]
Spiromycin	[illegible]
Viomycin	Used in treatment of cases of streptomycin resistant tuberculosis used combined with I N H
Cycloserine	Used in treatment of streptomycin resistant tuberculosis, usually combined with I N H
Isonicotinic Hydrazide (I N H)	Used in combination with P A S or streptomycin or dihydrostreptomycin in treatment of tuberculosis
Para amino Salicylic Acid (P A S)	Used with streptomycin or dihydrostreptomycin or with I N H in the treatment of tuberculosis
Pyrazinamide	Used only for treatment of tuberculosis
Kanamycin	Used only for treatment of other antibiotic resistant staphylococcic infections urinary tract infections
Vancomycin	Effective against staphylococcus intravenous route only

Clinical Application —Bacitracin has been used most widely and most successfully in the topical therapy of wound infections caused by *Staphylococcus aureus* and other gram positive bacteria particularly those microorganisms which are insensitive to other antibiotics This antibiotic should be used locally for the treatment of all penicillin-insensitive infections of wounds and systemically for penicillin-resistant staphylococci infections including meningitis and endocarditis The intramuscular dose is 15,000 to 20,000 units given 4 times a day

Toxicity —A limiting factor in the systemic or parenteral use of bacitracin is the risk of renal damage This is a variable manifestation but one that must be considered It is the one area which must be watched for signs of toxicity and

In view of the *high incidence of toxicity* neomycin is not an antibiotic with a high priority and it should not be selected as the first drug to be employed in any systemic infection

When it is used the oral dosage is 2 Gm every 6 hours and the parenteral dosage is 0 5 Gm every 6 hours

Polymyxin B (Aerosporin) —This antibiotic is derived from the micro organism *Bacillus polymyxin* It is a polypeptide and its main effect is against gram negative bacilli So far *it is one of the most powerful antibiotics against* these organisms although strains of Proteus are highly res stant

Polymyxin is not absorbed from the gastrointestinal tract but it eliminates sensitive organisms from the bowel when given by mouth When it is administered parenterally the intramuscular route is used and the total daily dose should not exceed 0 2 to 0 5 Gm The time interval between doses is 8 to 12 hours

Following parenteral injection the antibiotic is absorbed but disappears rap idly from the plasma It does not diffuse into the bile or cerebrospinal fluid and it cannot be detected in the urine in biologically active form

TOXICITY —A limiting factor in the use of polymyxin is its nephrotoxicity and its effects upon the nervous system In a certain number of patients beginning on *the fourth or fifth day proteinuria or oliguria with or without nitrogen retention* may appear The incidence of renal damage varies with the preparation with dosage and with the individual

The signs of nepthrotoxicity are those of paresthesias or numbness about the muzzle area The signs are temporary and usually disappear promptly with the withdrawal of the antibiotic

The most striking clinical results have been obtained in *Pseudomonas aeruginosa* infections especially bacteremia and in meningitis In the case of meningitis the antibiotic is given intrathecally in small dosages

In Pseudomonas infections of the urinary tract with systemic symptoms poly myxin should be used but with the understanding of its toxicity

Oleandomycin (Matromycin) —*This antibiotic is derived from Streptomyces antibioticus* and has been used most extensively in combination with tetracycline (Sigmamycin) for the treatment of penicillin resistant staphylococcic infections Oleandomycin is most active against gram positive bacteria but it has some effect against Neisseria Hemophilus and Brucella Also mycobacteria rickettsiae and some of the large viruses are inhibited slightly by its action It is active against staphylococci that are resistant *to other antibiotics but resistance develops with in* creasing concentrations of the antibiotic It has been used successfully in the treat ment of staphylococcic infections including enterocolitis and in bacterial pneumonias in children Likewise it has been effective in the treatment of gonorrhea soft tissue infections and donovanosis

It is given by mouth and the side effects are infrequent Absorption from the gastrointestinal tract is prompt and plasma concentrations of the antibiotic capable of inhibiting the growth of sensitive bacteria can be obtained with doses of 300 to 500 mg given in divided doses 3 to 4 times a day

The parenteral use of oleandomycin *is under experimental study in* staphylo coccic infections

fections if patients can take penicillin without reaction since penicillin is more active.

One of the interesting features of the agent is the rapidity with which resistant strains of staphylococci emerge after exposure to erythromycin either in vitro or in the management of patients There is some experimental evidence to indicate that the emergence of resistant strains may be delayed or diminished when organisms are exposed to mixtures of either penicillin or streptomycin, realizing, of course, that the original organisms are sensitive to both antibiotics at the start In any event, when erythromycin is given optimum doses should be employed for a short time and precautions taken against cross infection

This antibiotic is well tolerated and there are few if any side effects. The evidence of hypersensitivity is exceedingly low

Fumagillin —This antibiotic was first isolated as an antiphage agent from Aspergillus sp numbered H3 It was capable of inhibiting *Staphylococcus aureus* 209 bacteriophage but has no antiviral activity in vivo against viruses of poliomyelitis or influenza It has little or no activity against bacteria or fungi but it has been useful in the treatment of amebiasis in asymptomatic and mildly symptomatic patients It is the first antibiotic having a direct effect in *Entamoeba histolytica* and in many cases it has been of considerable merit in the treatment of intestinal amebiasis It is poorly absorbed from the intestine and has a low index of toxicity It is given orally in gelatin capsules and dosage schedules vary from 5 mg daily for 5 days to 50 mg daily in divided doses for 7 days

Signs of toxicity have been anorexia nausea and vomiting abdominal pain, drowsiness diarrhea vascular exanthems with desquamation and neutropenia

Kanamycin (Kantrex) —This antibiotic has been under clinical trial for the treatment of staphylococcic infections which are resistant to other antibiotics It is also being studied for the treatment of tuberculosis and urinary tract infections It resembles neomycin in its bacterial activity but it is less toxic It is readily absorbed when given by mouth and it may be given intramuscularly when necessary [Ototoxicity has recently been reported Ed]

Neomycin —Neomycin is a powerful bactericidal antibiotic with a broad spectrum It is active against a wide variety of gram positive and gram negative bacteria, but because of its toxicity it has a limited application It can be administered orally or parenterally or used locally in superficial wounds Absorption from the intestinal tract is poor This is one of the reasons that it is given orally for its local effect in reducing the bacterial flora of the intestinal tract prior to surgical operations on the large bowel as well as for nonspecific forms of diarrhea When neomycin is given by mouth in amounts of 2 Gm every 6 hours, the plasma concentration is only about one eighth as high as that which follows the intramuscular injection of only 0 5 Gm every 6 hours

The two signs of toxicity are renal injury and damage to the eighth cranial nerve The infections which have responded most often are *Proteus vulgaris* infections of the urinary tract or of wounds penicillin resistant staphylococcic infections and other antibiotic insensitive infections It has been used most widely as an agent to reduce the bacterial flora of the intestinal tract and in nonspecific diarrhea

vitro, and it shows no cross resistance with any other useful antibiotic The development of resistant strains of staphylococci under treatment has not been observed

Vancomycin is poorly absorbed from the intestinal tract and it is too irritating to be used intramuscularly therefore it must be given intravenously for systemic infections Following oral use gram positive organisms are eliminated from the *stools, but the* gram negative organisms continue to thrive After intravenous doses of 500 mg, effective plasma concentrations of the drug can be maintained for 12 hours therefore 2 daily doses are usually adequate The drug diffuses well into the tissues and high concentrations appear in the urine

The most favorable results have been reported in staphylococcic infections and in enterococcic endocarditis

Side effects have included chills fever skin rashes and phlebitis at the site of injection Granular casts have been observed in the urine during treatment but renal insufficiency has not been observed

Viomycin —This antibiotic has limited use for the treatment of tuberculosis It can be employed in patients who have become resistant to streptomycin and isoniazid *It is generally agreed* that it is less potent than other agents and should not be used in patients who have a streptomycin I N H sensitive infection However as a second or third line of defense it can be a useful agent in *the treatment of relapsing tuberculosis* due to organisms which are resistant to the more popular antibacterial drugs

The recommended dosage is 2 Gm injected intramuscularly every third day *preferably in combination with isoniazid or P A S It should* not be given as a companion with streptomycin because both drugs have an effect on the eighth cranial nerve and an additive toxic effect may occur

Intermittent therapy reduces the hazards of allergy and of eighth cranial nerve damage Also the disturbances in the plasma electrolytes that were reported are less frequent

THL SULFONAMIDES

The sulfonamides are exceedingly valuable agents in the treatment of a wide variety of infections and they have a wide application By careful selection of the proper sulfonamide many infections can be controlled

The limiting factors in the use of the sulfonamides are their side effects and the availability of antibiotics which in most infections are more active and effective The three most widely used and useful sulfonamides are sulfadiazine sulfamerazine and sulfisoxazole (Gantrisin)

All the sulfonamides can be given by mouth and with the exception of sulfaguanidine sulfathalidine and succinylsulfathiazole they are absorbed rapidly from *the gastrointestinal* tract Plasma concentrations of 5 to 10 mg per milliliter are usually adequate for the management of most infections

The two side effects which are most important are skin rashes with fever and *renal lesions leading to* oliguria and anemia The various side effects are discussed in the section on Side Reactions

[Recent studies have indicated that oleandomycin is relatively impotent and that in the form in which it is generally used a mixture with tetracycline (Sigmamycin), most if not all the therapeutic effects are produced by the tetracycline More recently, however, triacetyloleandomycin has been promoted and apparently used with more effect Ed]

Novobiocin (Cathomycin, Albamycin) —Novobiocin is produced from *Streptomyces spheroides* It is characterized as a potent narrow spectrum bactericidal antibiotic which is most active against staphylococci, including those resistant to other antibiotics, and against some strains of *Proteus vulgaris* and *Streptococcus faecalis* It is more active against gram positive bacteria than gram negative organisms but is less potent than other antibiotics

It is usually given by mouth in capsule form in doses of 1 to 2 Gm a day It is well tolerated and causes very few side effects About 5 per cent of patients become sensitized to novobiocin when it is given for a period of 7 days or longer the main features being fever and a skin eruption

Novobiocin is often combined with penicillin in order to broaden the spectrum of activity since novobiocin is effective against some organisms that are not susceptible to the action of penicillin alone

Following oral administration novobiocin is absorbed promptly from the gastrointestinal tract and it is excreted slowly over a period of 24 hours Adequate plasma concentrations of the drug can be obtained with doses of 250 mg given 4 times daily

Novobiocin is a useful agent for the treatment of staphylococcic infections some cases of *Proteus vulgaris* infections and enterococcic infections It is effective in other gram positive infections but less potent than other antibiotics

Ristocetin (Spontin) —This antibiotic is active against Gram positive bacteria and particularly against staphylococci When compared with vancomycin it is somewhat less active on a weight for weight basis Staphylococci develop resistance to ristocetin very slowly and it shows no cross resistance with other antibiotics

It is not absorbed from the gastrointenstinal tract and it is too irritating to be given intramuscularly The intravenous route must be used for the treatment of systemic infections It has been effective in the treatment of pneumococcal enterococcal and staphylococcal infections In general the agent is well tolerated except for local irritation at the site of injection Daily doses of 2 to 4 Gm or more in 2 to 4 injections are usually required in severe staphylococci infections

The drawbacks to the use of this antibiotic aside from the local irritating effects have been serious hematologic complications in some cases It is well then to reserve this antibiotic for the treatment of serious and life threatening staphylococcic infections in which other antibiotics have failed

Spiromycin —This is an antibiotic with a narrow bacterial spectrum and resembles novobiocin and erythromycin in its scope of activity Only a relatively small number of patients have been treated with it in the United States and it is not generally available

Vancomycin (Vancocin) —This is a bactericidal drug most effective against the staphylococci which are almost universally susceptible Resistance of staphylococci develops very slowly and with difficulty from exposures to vancomycin in

Streptomycin and dihydrostreptomycin have been discussed elsewhere The other useful drugs in the treatment of tuberculosis are presented here

Para Aminosalicylic Acid, Sodium Para-Aminosalicylic Acid —While this drug may be used alone for the treatment of tuberculosis, it is practically always used as a companion of streptomycin This agent interferes with the oxygen metabolism of the tubercle bacillus and is bacteriostatic against bovine and human strains as well as B C G This effect can be demonstrated in vitro and in vivo

When used alone, tubercle bacilli become resistant to it after several months When used in combination with streptomycin, there is a delay in the appearance of resistance to each of the two drugs So, for practical purposes when it is used, it is combined with streptomycin or with isoniazid

P A S has two limiting factors the gastrointestinal irritation and allergic reactions Also, in order to obtain an optimal effect, it is necessary to give between 12 and 20 Gm a day

DOSAGE —The minimum effective dose of P.A S is 8 Gm a day However, wide clinical experience has shown that the best results are obtained with doses ranging from 16 to 20 Gm a day If the sodium salt is used in patients who tolerate this salt better than P A S, then a dose 25 per cent greater should be used

The drug is given in divided doses, 4 times a day, usually with or after meals In this way it is better tolerated

The gastrointestinal symptoms are those of irritation and manifest themselves as anorexia, heartburn, and soft stools

Allergic reactions are shown by skin eruptions, fever, and occasionally localized pulmonary edema with eosinophilia

At present, P A S is usually combined with isoniazid rather than streptomycin It is agreed, however, that isoniazid as a companion of streptomycin is superior

Isoniazid and Related Compounds —

ISONIAZID (ISONICOTINIC ACID HYDRAZIDE, I N H) —This agent is a potent tuberculostatic agent which is similar to streptomycin It has the added advantage that it can be taken by mouth It is absorbed readily and diffuses into the cerebrospinal fluid in therapeutic concentrations It is therefore of great importance in the treatment of miliary tuberculosis and meningitis

It has the disadvantage when it is given alone that tubercle bacilli become resistant to it in the same way as to streptomycin, but when it is combined with streptomycin the emergence of resistant strains is greatly delayed and the therapeutic action of the combination is sustained for a long period of time Dosage schedules vary from 3 to 5 mg per kilogram of body weight to as much as 10 mg per kilogram when meningitis is present

In high doses, convulsions may be observed Toxic psychoses and peripheral neuritis and leukopenia have been reported, but especially when very high doses have been given

IPRONIAZID (ISOPROPYL ISONICOTINIC ACID HYDRAZIDE) —This drug was used before isoniazid The therapeutic effects of the two agents are similar, and there is cross resistance to the two drugs

It is rarely used today because of its toxicity It tends to produce toxic psychoses and disturbing and harassing withdrawal symptoms The difference in

Choice of Sulfonamides.—

SULFADIAZINE AND SULFAMERAZINE —These are the two sulfonamides of choice for the treatment of all cases of meningococcic meningitis meningococcic sepsis, and bacillary dysentery

SULFAPYRIDINE —Since dermatitis herpetiformis may be controlled by sulfa pyridine it should be used in all cases

SULFAGUANIDINE —This sulfonamide is highly effective in the treatment of some types of bacillary dysentery and in reducing the bacterial flora of the intestinal tract of patients who are being prepared for surgical procedures on the large intes tine Other sulfonamides such as succinylsulfathiazole and sulfathalidine are equally effective for the same type of surgical procedure

SULFISOXAZOLE (GANTRISIN – This sulfonamide is widely used for the treat ment of urinary tract infections because it is more soluble than either sulfadiazine or sulfamerazine It is readily absorbed from the gastrointestinal tract and is dis tributed in body water and does not enter cells It is acetylated to about 30 or 35 per cent but the acetylated form is more soluble in water than the other absorbable sulfonamides In view of the fact that it does not diffuse into cells the plasma concentration of Gantrisin is about three times that of other sulfonamides when equal amounts are given

SULFAMETHOXYPYRIDAZINE KYNEX MIDICEL) —This sulfonamide is well ab sorbed and slowly excreted The blood levels become high after a single oral dose and when as little as 0 5 Gm is given every 12 hours there is a tendency to ac cumulate during a period of 7 days and there is very little fluctuation between doses It is well tolerated and usually no untoward effects are encountered al though very recently accounts of serious adverse effects have been reported This agent may be most useful in the management of urinary tract infections and when prolonged treatment or prophylaxis is required

[There is insufficient evidence based on carefully controlled clinical experience to make a statement regarding the special merits if any of sulfadimethoxine (Madribon Madriqid) Ed]

SUMMARY —In short the sulfonamides are most useful in the control of menin gococcic and Shigella infections and in all urinary tract infections due to Gram negative bacteria Further they are exceedingly valuable in reducing the bacterial flora of the intestinal tract in preparation for surgical operations

TUBERCULOSTATIC DRUGS

There are available at present a number of tuberculostatic drugs which are highly effective for the treatment of tuberculosis Certainly, the physician is in a stronger position today when he is faced with the problem of treatment of tuber culosis than at any time in the past When he combines the best methods of the *past with the new advances in chemotherapy and surgery as indicated*, the patient benefits enormously

In general it can be said that tuberculosis is treated with a combination of drugs This is done for several reasons to reduce toxicity, to delay the emergence of resistant strains of tubercle bacilli and to achieve additive effects

systemic infections Experience with nitrofurans in urinary tract infections and elsewhere are discussed in appropriate chapters of this book Ed]

SIDE REACTIONS TO ANTIBACTERIAL AGENTS

Toxicity, General Comments —In the choice of any antibacterial agent it is necessary to be familiar with the toxic and harmful side effects which may be encountered The margin between toxic concentrations and therapeutic effects varies from one agent to another and in some instances it is very narrow indeed

When possible, these toxic and harmful side effects should be avoided at all costs because they may add an additional burden to the patient, especially to the resistance of an infant or an elderly person or to a person with a depression of resistance due to complicating diseases

Superinfection —One of the hazards of antibacterial therapy is the risk of superinfection by insensitive or resistant microorganisms This problem has been studied extensively by Weinstein and many others Briefly stated, the situation is as follows Following the use of antibacterial agents there is a profound alteration and disturbance of the normal bacterial equilibrium Some organisms are suppressed while others overgrow and predominate In many patients this alteration in the bacterial flora is unattended by any illness or signs of a superinfection, but any disturbance in equilibrium may cause serious illness in small infants, in elderly people, or in debilitated individuals

It is particularly noticeable that following the use of the broad spectrum antibiotics there is a suppression of the growth of the predominant natural flora of the respiratory and gastrointestinal tract There soon appears a group of organisms which are insensitive to treatment, namely, *Pseudomonas pyocyanea*, Proteus Candida These organisms are usually of very low virulence in the presence of normal host resistance, but they can be invasive and cause serious illness in infants and debilitated individuals

Weinstein found that superinfection was most often encountered in children under 3 years of age who had received one of the broad spectrum antibiotics The organs most often involved were those usually affected by the primary infection and the organisms responsible for the superinfection were more difficult to treat following the use of broad spectrum antibiotics than following the use of the narrow spectrum bactericidal antibiotics The common sites for reinfection were the respiratory tract, the middle ear, and the intestinal tract

Superinfections tend to occur most often on the fourth to fifth day after initiation of chemotherapy, they are often more protracted than the initial infection and are occasionally fatal

Alexander has directed attention to the fact that the rising incidence of meningitis due to Proteus and *Ps pyocyanea* is a consequence of the use of broad spectrum antibiotics

Forms of superinfection or hazardous side effects of antibiotic therapy, usually of the broad spectrum variety, are staphylococcus enterocolitis, monilial colitis, and pseudomembranous enterocolitis

It is well established that following the use of antibiotics, usually the broad spectrum ones, diarrhea may be a striking and troublesome feature *In some,*

the toxicity between the two drugs may be due not only to the difference in the chemical formula but also to the difference in the rate of absorption and the higher plasma concentrations that are observed when iproniazid is administered

PYRAZINAMIDE —This drug is pyrazine carboxamide and is a derivative of nicotinic acid Organisms become resistant to it at about the same rate as to I N H Also, I N H is more effective and less toxic One of the undesirable side effects is jaundice The dosage schedule is 2 8 Gm a day usually given in 700 mg doses, 4 times a day

The Sulfones —The sulfones have been used widely in the treatment of leprosy Basically, all of these compounds are derivatives of diaminodiphenyl sulfone They are Promin, Promizole, sulphetrone and hydroxyethyl sulfone Promin has been studied extensively in experimental tuberculosis in guinea pigs and is highly effective Promizole has been used widely in the treatment of miliary tuberculosis in infants and children and has been found to decrease the likelihood of relapse in miliary tuberculosis and tuberculous meningitis

Thiosemicarbazone (Amithiozone) —This chemical is more toxic and less effective in the treatment of tuberculosis than other available agents

Drugs of Choice —The drugs of choice for the treatment of tuberculosis, then may be listed as follows The first choice is streptomycin or dihydrostreptomycin with I N H The second choice is I N H and P A S Then cycloserine and I N H, and viomycin and I N H, and pyrazinamide and I N H may be used as a means of defense

Dosage Schedules —A wide variety of dosage schedules are recommended for the treatment of tuberculosis, and various patterns of treatment have been studied and are still being investigated The selection of agents the dosage schedules, and the duration of treatment require critical judgment and careful assessment of the individual patient—to include the location of the lesion and the general condition of the patient In the management of tuberculosis every detail must be considered and every patient assessed as a special and individual problem The patient must be followed carefully and regularly for a lifetime Therefore, the dosage schedules given here are presented as guide lines It is generally agreed that neither streptomycin nor isoniazid should be used alone because of the more rapid development of resistant strains

STREPTOMYCIN —The dose is 1 Gm every 2 to 3 days except in fulminating infections when 1 Gm a day should be used

DIHYDROSTREPTOMYCIN —Dosage is the same as for streptomycin

Five tenths gram of each may be used in combination instead of 1 Gm of either streptomycin or dihydrostreptomycin

P A S —Eight to twenty grams a day should be given in 4 divided doses When sodium salts are used 25 per cent more drug by weight should be used

ISONIAZID —The dose of I N H is 3 to 5 mg per kilogram of body weight, or 150 to 300 mg a day It is given in divided doses 2 or 3 times a day, usually by mouth It may be injected intramuscularly when patients are unable to take it by mouth This mode of administration may be useful in patients with meningitis

[There has not yet been sufficient experience with triclobisonium chloride (Triburon) and furaltadone (Altafur) for a valid opinion on their usefulness in

other sulfonamides Local application in the form of ointments to irritated skin induces high degrees of allergy and is undesirable In any event, when sulfonamides are used, one should be on the alert to detect reactions, especially fever and skin eruptions

PENICILLIN —Penicillin is the least toxic of all the antibiotics However, because of its widespread use the incidence of hypersensitivity or allergic reactions is increasing in frequency Some general principles are established and can be stated as follows The various penicillins tend to cross react in allergic patients, and the incidence of allergic reactions with various dosage forms is least when penicillin is given by mouth, greater with crystalline penicillin given by injection, greater still with procaine penicillin given by injection, and greatest of all when applied locally to inflamed skin in the form of ointments The procaine present in procaine penicillin rarely causes any reactions

The commonest reactions to penicillin are fever, skin rashes, urticaria, and serum sickness' syndrome, although acute shock or anaphylactic reactions may be observed if penicillin is accidentally injected into a vein in an allergic patient An infrequent reaction is a polyarthritis

One may observe eosinophilia without other signs of hypersensitivity, and when penicillin is used locally in the mouth, dryness and soreness of the tongue are often a complaint Black tongue is an occasional feature

Convulsions and coma may be observed following the injection of penicillin intrathecally, and if this route of administration is used, not more than 5,000 to 15,000 units should be injected in a 24 hour period

[The utility of penicillinase (Neutrapen) in the treatment of penicillin reactions has not yet been established Ed]

STREPTOMYCIN —There are two common reactions following streptomycin—hypersensitive reactions and neurologic complications such as vertigo, tinnitus, and deafness The hypersensitive reactions are not serious, but they tend to be relatively frequent, perhaps because streptomycin is used for treatment of tuberculosis and is given for protracted periods of time

The three symptoms referable to the eighth cranial nerve following streptomycin are tinnitus, vertigo and deafness They are infrequent now that the dosage of streptomycin and the frequency of its administration for the treatment of tuberculosis have been decreased The symptoms may be mild or severe They may be transitory and disappear with discontinuing the antibiotic Occasionally the labyrinthine disturbance and the deafness are permanent

THE TETRACYCLINES —These antibiotics are usually well tolerated and the incidence of hypersensitive reactions is low, the common symptoms being fever and skin rashes Inasmuch as these agents are closely related chemically, they probably cross react in allergic patients

The chief side effects of these agents are nausea vomiting, diarrhea, and epigastric distress Some patients complain of a metallic taste in the mouth and lose the sense of smell Pruritus of the anus or scrotum and vaginitis may be most troublesome and annoying

The most troublesome side effect is diarrhea which may be due to one of several factors first, the direct irritative effect of the antibiotic on the intestinal

Micrococcus pyogenes is cultured in pure culture, in others no micrococci are found The problem is a complex one because antibiotic resistant strains of *M pyogenes* may be present, along with the normal intestinal flora, and produce no symptoms On the other hand, when they occur in large numbers or in pure culture, they may be associated with the systemic reactions and the diarrhea that has been so clearly described by Finland Micrococcic enteritis is a reversible disease and often can be treated adequately with erythromycin novobiocin, or neomycin

Pseudomembranous enteritis or enterocolitis is a more serious disease and may exist with or without *M pyogenes* in the intestine and with or without previous antibiotic therapy The relation between *M pyogenes* and pseudomembranous enteritis or enterocolitis remains unclear When *M pyogenes* is present in the stools of these patients, then suppression may be followed by improvement This subject has been studied and reviewed by Finland Deany and others

Allergy and Other Reactions—One of the common problems concerned with the use of antibacterial agents is the undesirable side reactions which may follow They vary with the drug used and with the individual It is necessary to be familiar with the types of reaction that may occur so that they may be recognized and treated Allergic reactions to drugs have been discussed briefly but clearly in a paper by Lowell in which he has made many practical points

The subject is a broad one and there are many gaps in our knowledge concerning the various reactions which are observed Lowell has summarized the types of reactions into allergic, probably allergic and possibly or doubtfully allergic They are listed in Table 12

*Table 12 List of Allergic or Possibly Allergic Reactions to Drugs**

(A) Allergic	(B) Probably Allergic	(C) Possibly or Doubtfully Allergic
1 Rash usually maculopapular but variable and often associated with fever	1 Fever alone	1 Leucopenia
2 Urticaria and angioneurotic edema	2 Purpura (often not thrombocytopenic)	2 Anemia
3 "Serum disease syndrome	3 Granulocytopenia	3 Nephritis or nephrosis
4 Exfoliative dermatitis	4 Necrotizing angiitis (including polyarteritis)	4 Hepatitis
5 Eosinophilia	5 Syndrome simulating disseminated lupus erythematosus	5 Aplastic anemia
6 Acute allergic or 'anaphylactic' shock asthma and urticaria, in combination or singly		6 Acute hemolytic anemia
		7 Peripheral neuritis
		8 Fibrinous pneumonia

*From Lowell Allergic Reactions to Drugs The Practitioner 178 673, 1957

The various reactions to antibacterial agents will be summarized here

The Sulfonamides—The sulfonamides tend to produce reactions in a moderate number of patients who receive them The commonest types of reaction are fever and a skin eruption The skin eruption is usually maculopapular in type but other skin reactions such as urticaria, angioneurotic edema, and exfoliative dermatitis may occur Serum sickness syndrome, purpura, granulocytopenia necrotizing angiitis, anemia, nephrosis, and hepatitis are seen less often

It is generally acknowledged that sulfathiazole, or all sulfonamides that are hydrolyzed to sulfathiazole, cause rashes and other reactions more often than the

other sulfonamides Local application in the form of ointments to irritated skin induces high degrees of allergy and is undesirable In any event, when sulfonamides are used one should be on the alert to detect reactions, especially fever and skin eruptions

PENICILLIN —Penicillin is the least toxic of all the antibiotics However, because of its widespread use the incidence of hypersensitivity or allergic reactions is increasing in frequency Some general principles are established and can be stated as follows The various penicillins tend to cross react in allergic patients, and the incidence of allergic reactions with various dosage forms is least when penicillin is given by mouth, greater with crystalline penicillin given by injection, greater still with procaine penicillin given by injection, and greatest of all when applied locally to inflamed skin in the form of ointments The procaine present in procaine penicillin rarely causes any reactions

The commonest reactions to penicillin are fever, skin rashes, urticaria, and serum sickness syndrome, although acute shock or anaphylactic reactions may be observed if penicillin is accidentally injected into a vein in an allergic patient An infrequent reaction is a polyarthritis

One may observe eosinophilia without other signs of hypersensitivity, and when penicillin is used locally in the mouth dryness and soreness of the tongue are often a complaint Black tongue is an occasional feature

Convulsions and coma may be observed following the injection of penicillin intrathecally, and if this route of administration is used, not more than 5,000 to 15,000 units should be injected in a 24 hour period

[The utility of penicillinase (Neutrapen) in the treatment of penicillin reactions has not yet been established Ed]

STREPTOMYCIN —There are two common reactions following streptomycin—hypersensitive reactions and neurologic complications such as vertigo, tinnitus and deafness The hypersensitive reactions are not serious but they tend to be relatively frequent, perhaps because streptomycin is used for treatment of tuberculosis and is given for protracted periods of time

The three symptoms referable to the eighth cranial nerve following streptomycin are tinnitus vertigo and deafness They are infrequent now that the dosage of streptomycin and the frequency of its administration for the treatment of tuberculosis have been decreased The symptoms may be mild or severe They may be transitory and disappear with discontinuing the antibiotic Occasionally the labyrinthine disturbance and the deafness are permanent

THE TETRACYCLINES —These antibiotics are usually well tolerated and the incidence of hypersensitive reactions is low, the common symptoms being fever and skin rashes Inasmuch as these agents are closely related chemically, they probably cross react in allergic patients

The chief side effects of these agents are nausea vomiting diarrhea and epigastric distress Some patients complain of a metallic taste in the mouth and lose the sense of smell Pruritus of the anus or scrotum and vaginitis may be most troublesome and annoying

The most troublesome side effect is diarrhea which may be due to one of several factors first, the direct irritative effect of the antibiotic on the intestinal

mucosa second a change in the bacterial flora with a superinfection with tetracycline resistant staphylococci and/or moniliasis and finally a severe form of diarrhea caused by pseudomembranous colitis which may appear independent of antibiotic therapy but which is seen today most often in patients who have received antibiotic therapy

It is desirable in every case to establish the cause of diarrhea in order to institute proper treatment When diarrhea is caused by the direct action of the drug the dosage schedule has usually been greater than 1 Gm a day, and therefore the reduction of the total dosage or discontinuance of the antibiotic is an effective measure of control

When staphylococcic diarrhea is present the stools commonly contain a pure culture of staphylococci which are resistant to the antibiotic that is being used The superinfection may be controlled by stopping the antibiotic and by giving either novobiocin or erythromycin

When the monilia predominate nystatin should be used

Chloramphenicol.—This antibiotic is well tolerated and the incidence of reactions is low Skin rashes and fever have been reported Lower abdominal cramps and discomfort nausea vomiting and diarrhea occur in occasional patients

Because of the occasional occurrence of aplastic anemia or agranulocytosis which may be fatal there has been a tendency to use this drug less than other antibiotics When it is used the patient should be followed carefully and leukocyte and erythrocyte counts done regularly

Bacitracin —The chief problem in using this antibiotic is the occurrence of renal insufficiency Albuminuria and nitrogen retention may occur Other side effects are infrequent although skin eruptions tinnitus nausea and vomiting and occasional disturbances in taste are noticeable

Carbomycin and Erythromycin These two antibiotics are closely related in their action against bacteria and often show cross resistance They are well tolerated and the incidence of reactions is very low Occasional skin rashes have been recorded Otherwise few if any side reactions have been noted

Neomycin The one drawback to using this antibiotic systemically is the high incidence of side effects It is well tolerated when used locally or when given by mouth because very little is absorbed

The side effects recorded have been renal irritation with proteinuria and cylindruria renal insufficiency dizziness and tinnitus numbness of the hands and feet or face and low grade fever

Novobiocin —The side reactions of novobiocin are limited to skin rashes although rare cases of leukopenia have been recorded

Nystatin —This agent is usually combined with one of the tetracyclines and given by mouth Side effects are few and those which are recorded consist of flatulence nausea diarrhea and diaphoresis Systemic reactions are not recorded

Oleandomycin —This antibiotic is well tolerated and is used most often in combination with tetracycline (Sigmamycin) It is given by mouth and readily absorbed from the gastrointestinal tract Apparently triacetyloleandomycin is to be preferred

POLYMYXIN B (AEROSPORIN) —The side effects of polymyxin B consist of renal irritation with albuminuria, *cylindruria and nitrogen retention, fever, vertigo,* and paresthesia of the fifth cranial nerve, especially around the mouth

SPIROMYCIN —The side effects of this agent are minimal and are usually mild gastrointestinal symptoms

[TRIACETYLOLEANDOMYCIN —It may be that this agent accomplishes what was hoped for with oleandomycin Much more experience is needed Ed]

VANCOMYCIN —Very few toxic reactions have been reported, but not many patients have been treated

VIOMYCIN —This antituberculostatic agent causes eighth cranial nerve lesions *and allergic manifestations Vestibular disturbances* and impaired hearing may result from prolonged use

CYCLOSERINE (SEROMYCIN) —This antibiotic is used for the treatment of tuberculosis and is usually combined with isoniazid The significant side effects are referable to the nervous system Personality changes, convulsions, and hyper reflexia are the features observed These irritative phenomena are related to the total dosage, the plasma concentration, and the pre existing convulsive tendencies and/or personality disorders of the patient They appear most often when the dosage has been more than 1 Gm per day, and they are more frequent when the entire dose is given at one time rather than being divided

When it is combined with isoniazid, it should be recalled that this agent alone *may cause signs of central nervous system stimulation* Doses of 0 5 Gm of cycloserine divided in two doses and isoniazid in dosage of 4 mg per kilogram of body *weight may be utilized without signs of drug toxicity*

PARA AMINOSALICYLIC ACID—P A S —The two most important side effects following the use of P A S are gastrointestinal symptoms and the development of hypersensitivity in some patients Anorexia, indigestion, and loose stools are the common gastrointestinal complaints, and skin rashes and fever the common allergic features

ISONICOTINIC HYDRAZIDE—I N H —When large doses are used, symptoms of central nervous system irritation may be observed Hyperreflexia and convulsions may occur in high dosage

SELECTED REFERENCES

Bunn, P A, Canarile, L, and Eastman, G Pharmacologic *Properties of Various Anti microbial Agents With Particular Reference to Common Dosage Scheduling,* New York J Med 55 3607, 1955

Dowling, H F Mixtures of Antibiotics J A M A 164 44, 1957

Finland, M Antimicrobial Treatment for Viral and Related Infections New England J Med 247 317 1952

[illegible] Endocarditis J A M A 166 364 1958

[illegible] M Cross Resistance to Antibiotics [illegible] in or Erythromycin in Vitro Proc Soc [illegible]

[illegible] nbinations, New England J Med 256 [illegible]

[illegible] lococci, South M J 49 1173 1950

Lin, F, and Cohen, [illegible] [illegible] Antibiotics on the in Vitro Emergence *of Staphylococci Resistant to Novobiocin,* AM & CT 4 35 1957

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THE CHOICE OF DRUGS FOR VIRAL, SPIROCHETAL, AND RICKETTSIAL INFECTIONS

Leighton E. Cluff, M.D.

INTRODUCTION

Several microbial diseases, such as smallpox and typhus, once played an important role in the political, military, economic, and social life of nations but have become medical oddities in many parts of the world The decreased significance of these infections is attributable largely to improved standards of public health, associated with effective control of the dissemination of microorganisms, better methods of sanitation, elimination of vectors of disease, prophylactic immunization, and rising standards of living and education Chemotherapeutic agents and antibiotics have had an impact upon some of these infections and have been at least partly responsible for the changed spectrum of microbial disease

The pestilences of the past have been replaced by infections not appreciably affected by therapy, and, although a few bacterial diseases are involved, the infections resistant to drug treatment are caused largely by viruses It is fortunate, in this respect, that many of the virus infections which are a serious threat to life, including epidemic influenza, poliomyelitis, smallpox, and rabies, are being controlled by vaccination Although occasionally effectively prevented by immunization, the rickettsial and spirochetal infections are often vulnerable to antibiotic treatment and, therefore, successfully met Despite these advances in prophylaxis and treatment of infection, we have yet to understand the means of preventing or treating the commonest of all human infections—the "common cold" This is illustrative of the fact that the infections presently most difficult to deal with are those in which man is the principal natural reservoir and the disease is spread from person to person by direct contact or by the respiratory route Interruption of the spread of infection can then be accomplished primarily by immunization, and, when this is unsuccessful, the disease may continue to occur Treatment of an infection such as syphilis with drugs has occasionally been an effective means of preventing spread to other persons, but this has not been a uniform experience Spread of infection becomes less serious, however, when the disease is benign or when an effective therapeutic agent is available For example, we often encourage the transmission of common contagious diseases such as rubella, rubeola, and

Lowell, F C Allergic Reactions to Drugs Practitioner 178 673, 1957
MacLeod, C M Interactions of Host, Microbe and Chemotherapeutic Agent, Bull New York Acad Med 31 427, 1955
Marshall, E K, Jr The Dosage Schedule of Chemotherapeutic Agents, Pharmacol Rev 4 85 1952
Marti Ibanez, F The Next Half Century in Antibiotic Medicine and Its Impact on the History of the Clinical Case History, Antibiotics Annual 1955 1956, p 3
Modell, Walter The Comparative Effectiveness and Selection of Sulfonamides and Antibiotics, Pharmacology in Medicine, ed 2, New York, 1958 McGraw Hill
Perry, H O, and Winkleman R K Adverse Reactions to Sulfamethoxypyridazine (Kynex), J A M A 169 127, 1959
Salvaggio, J and Gonzalez, F Severe Toxic Reactions Associated With Sulfamethoxypyridazine (Kynex) Ann Int Med 51 60, 1959
Stone, R L, Boniece, W S, and Culbertson, C G A Comparison of the in Vitro and in Vivo Effects of Erythromycin, Penicillin and Oxytetracycline Against Resistant Staphylococci Antibiotics and Chemotherapy 5 17, 1955
Wier J A Present Status of the Treatment of Tuberculosis, J A M A 162 471, 1956
Wyss O, Smith G N, Hobby, G L, Oginsky, E L, and Pratt, R Symposium on the Mode of Action of Antibiotics, Bact Rev 17 17, 1953

observed after institution of treatment may be unrelated to the therapy Fig 2 illustrates an instance of Q fever where defervescence occurred without antibiotic treatment and before confirmation of the diagnosis by serologic test was possible

Syphilis is an example of an infection frequently unassociated with significant illness during the acute primary disease but is followed by serious late complications A few of the rickettsial infections may be relapsing in character In an acute infection that is asymptomatic or characterized by spontaneous recovery, the danger of recrudescence or late complications may, in certain instances, demand treatment On the other hand, if relapses and late sequelae do not present a problem, as in Q fever, treatment following spontaneous recovery is not necessary An

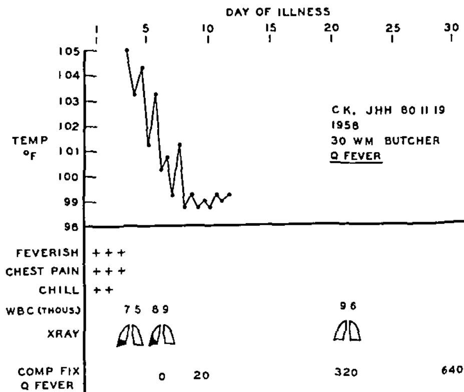


Fig 2 —The course of untreated Q fever in a butcher, showing rapid spontaneous defervescence

awareness of the natural history of the infection when no specific therapy is given will obviously determine to a large degree the appropriate use of drugs

Antimicrobial drugs have limited *effectiveness in the treatment* of irreversible

lished, as illustrated by the failure of penicillin in the treat

once impaired hepatic function has become evident These facts are of importance in considering the application of antibiotics in the treatment of infection

A Design for the Use of Nonspecific Therapy —Fever, shock, respiratory difficulty, cardiac failure, and other manifestations of infection are not controllable

varicella from child to child to 'get it over with,' and we may make little effort to vaccinate exposed persons to Q fever, since the disease is so susceptible to treatment with several antibiotics. These considerations condition one's expectations from newer drugs which will undoubtedly become available in the future for treating infections, particularly those due to viruses Although drugs might be successful in treating infection, they may abort the development of effective immunity or have no particular influence upon the occurrence of disease

Prophylactic use of antibiotics has been successful in certain instances, but the impracticality of widespread use of such a measure is clearly evident In the rickettsial diseases, prophylactic antibiotics may only prolong the incubation period of the infection but not prevent the illness

The broad generalizations made above in no way negate the importance of drug treatment of infectious disease The armamentarium in antibiotics now available has saved lives and significantly reduced the seriousness of many infections, but their use has not eliminated the necessity of considering the ecologic relationships in microbial disease

CLINICAL APPLICATIONS

Selection of an antibiotic or other chemotherapeutic agent in the treatment of an infection is dependent upon a correct diagnosis There is no generally effective drug that can be selected indiscriminately in the therapy of an undiagnosed infection The microbiologic laboratory has played an important part in the diagnosis of bacterial diseases but has yet to become very useful in identification of the microorganisms responsible for viral, rickettsial, or spirochetal infections. Demonstration of *Treponema pallidum* in the primary chancre of syphilis and detection of inclusion bodies in varicella are two of the very few examples of these infections where the microorganisms can be readily identified

It is evident that for a specific drug to be maximally effective in the treatment of infection, it is best given early in the course of disease This fact is [illegible] that serologic tests are of little value in directing the therapy of infection. Furthermore, the many serologic tests now available for diagnostic purposes [illegible] a discriminating clinical impression for selection of the appropriate confirmatory test Demonstration of serum antibody, however, is frequently the [illegible] available for finally establishing a correct diagnosis and categorizing [illegible] characteristics and epidemiology of disease

Fortunately, many viral, spirochetal, and rickettsial infections [illegible] ing clinical and epidemiologic characteristics that facilitate their recognition. [illegible] myelitis, for example, may be unrecognized when it occurs sporadically [illegible] it occurs in an epidemic, identification of the infection is greatly enhanced. Clinical experience, interest, and a high index of suspicion are, therefore [illegible] portance in the diagnosis of these infections

Evaluation of the effectiveness of a drug in the treatment [illegible] must include an understanding of the natural course of the [illegible] Many of the viral, rickettsial, and spirochetal infections are self-limited and recovery may occur spontaneously and rapidly When this happens [illegible]

pyretics When aspirin (acetylsalicylic acid) is given as an antipyretic, it should be administered at regular intervals and in doses sufficient to reduce the temperature without necessarily rendering the patient afebrile Aspirin in a dosage of 0 3 to 0 6 Gm given every 3 to 4 hours will ordinarily accomplish the desired effect The adrenal corticosteroids may reduce the fever of infection but should never be used solely for this purpose

Vascular collapse with hypotension is observed occasionally in many severe infections, and its treatment is little different from that used in other forms of nonhemorrhagic shock Although blood transfusions are not ordinarily necessary, in the rickettsial infections hypoproteinemia and electrolyte disturbance are common, and blood or plasma, as well as electrolyte infusions, has been said to be of value

Norepinephrine is a useful drug for maintenance of blood pressure in the vascular collapse associated with infection and should be given as an intravenous infusion of 5 per cent glucose and 0 85 per cent NaCl containing 4 to 8 mg norepinephrine per liter The rate of administration will be determined largely by the response of the patient s blood pressure Adrenal insufficiency is probably a rare complication of viral rickettsial and spirochetal infections, but the adrenal corticosteroids can have a beneficial influence upon the vascular collapse seen in these diseases Preparations are available for parenteral and oral administration, but in the presence of shock intravenous therapy is usually necessary Hydrocortisone may be given intravenously in an infusion of glucose and saline containing 100 mg or more of the drug Prednisone or prednisolone may be given orally in a dosage of 25 to 50 mg or more per 24 hours Combined use of corticosteroids and vasopressor agents, such as norepinephrine, may be more effective than either agent alone in controlling vascular collapse The pharmacologic action of corticosteroids in restoring normal vascular tone in the shock of infection is not known Inhibition of the injurious effect of certain microbial toxins and reduction of inflammation by the hormones may be important mechanisms, but their influence upon electrolyte metabolism and their demonstrated action upon vascular reactivity may also be responsible for correcting hypotension The place of adrenal steroids in the management of infections, however, has not yet been completely established It is of course, important to be alert to more specific causes of shock in infection particularly that attributable to myocardial or respiratory failure

Respiratory insufficiency and cyanosis can develop in several of the infections under consideration They are attributable to pneumonia and bronchitis observed in psittacosis, primary atypical pneumonia, Q fever, influenza, and varicella or they are attributable to respiratory paralysis as observed in poliomyelitis Embarrassment of pulmonary function may develop from bronchial obstruction, disturbance of alveolocapillary gas diffusion, or from weakness of the muscles of respiration Bronchial obstruction is not commonly observed in the pulmonary involvement associated with viral, spirochetal, and rickettsial infections unless bronchial asthma develops or there is secondary bacterial infection Bronchodilators such as aminophylline or epinephrine may be effective in alleviating bronchial obstruction, but the inhalation of moisture laden air (steam) is particularly useful in facilitating the removal of thick bronchial secretions and relieving cough in tracheitis, as may

entirely by specific antibiotic therapy It is, therefore, necessary in considering the treatment of choice in infection to employ drugs of value in the management of these manifestations or complications Many of the symptomatic remedies are discussed separately elsewhere and will not be considered

Fever is a constant occurrence in most viral, rickettsial, and spirochetal infections but is rarely of sufficient magnitude to require the use of antipyretics Artificial reduction of fever, however, may be desirable in the patient who could be

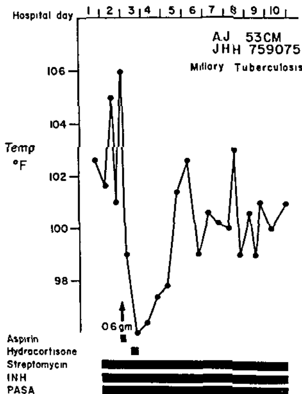


Fig 3—Abrupt, severe, and transient hypothermia in a patient with miliary tuberculosis following a single oral dose of aspirin

adversely affected by high temperature Administration of antipyretics to febrile patients may be followed occasionally by an abrupt fall in temperature producing transient hypothermia (Fig 3) Their intermittent use, therefore, can result in a hectic febrile course leading to repeated chills and exhaustion Sporadic use of antipyretics is undesirable, not only because of the possible production of chills and hypothermia but also because changes in the febrile pattern may eliminate a most important criterion of diagnosis and prognosis

Salicylates, particularly aspirin, are most frequently used for control of fever in infection, although the adrenal corticosteroids also have been in vogue as anti

prove incomplete or inadequate Relapse of infection or failure to prevent the occurrence of disease after administration of a bacteriostatic antibiotic has been observed in rickettsial infections and is illustrative of the inadequacy of such treatment Unfortunately, however, reliance must be placed at present upon rickettsiostatic drugs for the specific therapy of these infections, since no rickettsiocidal antibiotic is available Penicillin has little, if any, action upon rickettsiae but is of value in treatment of many of the spirochetal infections

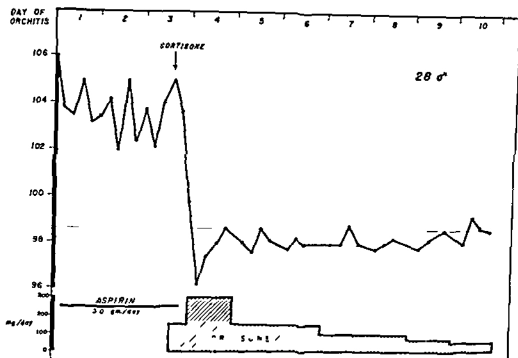


Fig 4—The effect of hydrocortisone upon the fever in a patient with mumps orchitis associated with prompt alleviation of testicular pain

Prophylaxis—Antibiotics have been used excessively in the prophylaxis or prevention of infection Their administration for this purpose, however, is circumscribed and is indicated and effective only in specific instances The rapidly accumulating evidence illustrates clearly the inadvisability of the indiscriminate use of antibiotics for prophylaxis

Penicillin will prevent the development of syphilis in the exposed person, but if the dosage of the drug is inadequate the infection may be aborted but not eliminated Ordinarily 1 to 2 million units of procaine or benzathine penicillin G will protect against the development of syphilis, but the exposed person must be followed closely with serologic tests during the 6 months after contact with the infected subject *Whether or not the administration of tetracycline or penicillin will prevent the development of psittacosis or lymphopathia venereum after exposure is not known, and the influence of prophylactic* antibiotics upon other spirochetal infections has not been assessed

be observed in varicella and influenza Tachypnea and cyanosis attributable to alveolar involvement are occasionally seen in primary atypical pneumonia, influenza pneumonia, varicella and other virus and rickettsial infections Oxygen, of course is a useful adjunctive treatment in patients with these infections, but will not aid in the resolution of the disease process Adrenal corticosteroids have been useful agents in some instances of diffuse pulmonary infection without apparent harm It has been suggested however, that varicella developing in the person receiving adrenal steroids may be very severe The beneficial effect of cortisone upon the pneumonia due to viral and rickettsial infections however, has not yet been conclusively demonstrated Maintenance of the respiratory toilet and use of the artificial respirator are of primary importance in relieving the disturbed pulmonary function associated with poliomyelitis

The adrenal corticosteroids undoubtedly have a nonspecific but important place in the management of many infections The potentially deleterious influence of these hormones in microbial diseases has been repeatedly stressed, however, and their eventual role in treatment has yet to be defined There can be no question about the use of adrenal steroids in the presence of adrenocortical insufficiency, but the hormone dosage required to significantly change the course of an infection far exceeds that used for replacement therapy In those infections for which effective specific antimicrobial drugs are available, cortisone has been found to be a useful therapeutic adjunct in relieving the symptoms of infection and in ameliorating complications When no specific antimicrobial agent is available, however the possible adverse effects of steroids upon the infection must be weighed against the beneficial influence of the hormones upon symptoms or complications of the disease

Mumps orchitis can frequently be dramatically relieved with corticosteroids Initiation of cortisone treatment is followed by prompt defervescence and alleviation of testicular pain (Fig 4) Interstitial keratitis and eighth cranial nerve deafness developing in congenital or late syphilis do not respond to antibiotic treatment but the administration of adrenal steroids may be accompanied by the clearing of the keratitis and the return of hearing Similarly, the nerve deafness rarely observed in persons convalescing from influenza has improved with corticosteroid therapy Severe fulminant hepatitis has been reported to respond favorably to cortisone treatment but the beneficial influence of this therapy is inconstant Other manifestations of viral, rickettsial, and spirochetal infection have been treated with corticosteroids but the effectiveness of such therapy has not been established

A Design for the Use of Specific Antibiotics —Drugs which suppress microbial multiplication must be differentiated from drugs capable of killing microorganisms Virtually all antibiotics have both bacteriostatic and bactericidal activity, but achievable therapeutic blood levels of the antibiotics commonly referred to as broad spectrums are principally bacteriostatic Penicillin is the one drug available which can be administered in almost unlimited quantity and is usually bactericidal against those organisms it is capable of affecting The distinction between these types of antimicrobial agents is important, since killing of the microorganism by the drug can eradicate infection independent of mechanisms of host resistance, whereas suppression of the infection may not eliminate the disease if host defenses

4 Gm a day The occurrence of serious reactions to sulfonamides, such as periarteritis nodosa, drug fever, dermatitis medicamentosa, and hematologic disorders, may eventually lead to the uniform acceptance of tetracycline as the drug of choice in this infection

The sulfonamides and tetracycline drugs are effective in the treatment of trachoma as they are in psittacosis and lymphopathia venereum The dosage of these drugs in trachoma is the same as in the latter two virus infections Tetracycline has one demonstrated superiority over sulfonamide in the treatment of this infection, namely, its greater effect in treatment of the infection by topical application as an ointment to the eye

Although reports have appeared from time to time indicating that the bacteriostatic antibiotics, such as tetracycline, are effective in shortening the illness associated with primary atypical pneumonia, herpes zoster, infectious hepatitis, and infectious mononucleosis, there is insufficient evidence to enable a recommendation of these drugs in treatment of virus infections except psittacosis, lymphopathia venereum, and trachoma There are no drugs of demonstrated value in the specific treatment of rabies, poliomyelitis, influenza, or other virus diseases Therefore, reliance must be placed upon biologicals such as antiserum and vaccines, and upon drugs for control of symptoms in these infections

The bacteriostatic antibiotics, particularly chloramphenicol but also tetracycline, are effective in treatment of the rickettsial infections, including Rocky Mountain spotted fever typhus, Q fever, and rickettsialpox The usual dosage of these drugs in adults is 3 to 4 Gm per day in 3 to 4 divided doses In children the dosage may be correspondingly reduced, depending upon the weight of the patient As a general rule 25 mg per kilogram of body weight can be administered This treatment is most effective when begun early in the course of illness when the mortality rate from the infections can be eliminated and the duration of disease shortened to about one sixth of that observed in the untreated person It is desirable that treatment be continued until the patient is symptomatically improved and the temperature has been normal for 2 or more days Relapse of infection is uncommon if specific treatment is begun early and continued long enough, but in scrub typhus recrudescence of fever may appear 5 to 8 days after discontinuing the antibiotic Reinstitution of therapy is followed again by prompt recovery Antibiotics other than chloramphenicol and tetracycline have not been demonstrated to be effective in the rickettsial infections

Many of the antibiotics have a bactericidal or bacteriostatic action upon the spirochetes responsible for syphilis, Weil's disease relapsing fever, and rat bite fever

Chloramphenicol, tetracycline, and erythromycin have a treponemicidal effect, but penicillin is generally considered the drug of choice in the treatment of syphilis The depot, or long acting penicillin preparations are most frequently used primarily because of their greater ease of administration, but also because they are known to be effective in antisyphilitic therapy

Early syphilis can be treated adequately with 4 to 6 million units of procaine penicillin given in divided daily doses over a period of 8 to 10 days Intramuscular benzathine penicillin G can be given as a single dose of 2 5 million units and has the advantage of providing effective therapy with one injection, but it is not

The ineffectiveness of prophylaxis with a rickettsiostatic antibiotic such as tetracycline in preventing the emergence of disease in volunteers exposed to *Coxiella burnetii* has been described Although illness did not appear in the exposed persons while the drug was given, withdrawal of the antibiotic was followed by development of Q fever The incubation period of the disease was merely prolonged A similar example of the ineffectiveness of bacteriostatic antibiotics in preventing the occurrence of tularemia in volunteers has been described In the latter circumstance, however, complete suppression of the infection was possible when bactericidal streptomycin was used as the prophylactic agent It is probable that a rickettsiocidal drug would be equally effective in the prevention of Q fever

The administration of antibiotics or sulfonamides to patients with virus infections in an attempt to prevent secondary bacterial infection has been a common practice but is usually ineffective and cannot be condoned Antibiotics cannot prevent the development of *all* bacterial infections although prophylaxis directed against specific infections, such as those due to group A Streptococcus, Pneumococcus, and Shigella may be successful The incidence of secondary infection is probably not changed, but the invading bacteria will be commonly resistant to chemotherapy in virus infections treated with prophylactic antibiotics

Controlled studies of the use of antibiotics to prevent secondary bacterial infection in patients with measles and poliomyelitis have shown no decrease in the occurrence of bacterial complications, but the secondary infections were almost uniformly attributable to antibiotic resistant *Pseudomonas pyocyanea, Staphylococcus aureus,* and *Hemophilus influenzae* Bacterial infections in patients with poliomyelitis who did not receive prophylactic antibiotics were most often attributable to antibiotic sensitive pneumococci and beta hemolytic streptococci

When it is desirable to prevent the appearance of group A streptococcal or pneumococcal infections in patients with virus disease, particularly of the respiratory tract, *small* doses of procaine penicillin G (300 000 units) or oral penicillin G (600,000 units) may be given each day This prophylactic treatment, however, must not be given with the expectation of preventing *all* secondary bacterial infections Preferably, the secondary infection should be treated appropriately when and if it occurs

Specific Treatment —Psittacosis, lymphopathia venereum, and trachoma are notable exceptions to the rule that virus infections are not susceptible to antibiotic therapy Many of the available antibiotics are effective in the treatment of psittacosis including penicillin given in large doses The tetracyclines are the preferred drugs, however, in this disease, and 2 to 4 Gm given by mouth in 4 divided doses every 24 hours will ordinarily eliminate the infection *Treatment should be continued* until the patient has been afebrile for 3 to 4 days

The acute manifestations of lymphopathia venereum usually respond to treatment with sulfonamides although resolution of the infection may not occur for 1 to 2 weeks after beginning therapy Four grams of sulfadiazine per day, given in divided doses, is the accepted drug schedule for the disease Other absorbable sulfonamides are probably as effective as sulfadiazine, but they have been used less frequently Bacteriostatic antibiotics, such as tetracycline and chloramphenicol, are also effective in treatment of lymphopathia venereum, in divided doses of 2 to

The classical treatment of rat-bite fever (caused by *Spirillum minus*) is with arsenical preparations Recent experience, however, indicates that penicillin and tetracycline may be the drugs of choice in this infection Five million units of penicillin, or 3 to 4 Gm of tetracycline, given every day is usually effective in controlling the disease

Relapsing fever is a relatively infrequent disease in the United States and occurs predominantly in the western part of the country Treatment of this infection with 2 to 4 Gm of tetracycline per day is usually effective

GENERAL PHARMACOLOGIC CONSIDERATIONS AND THE VARIOUS DRUGS

Antibiotics have the impressive property of affecting viable cells differentially Although toxic in therapeutic doses for susceptible microorganisms, they have little influence upon the host's tissues This is particularly true with penicillin, as this antibiotic can be administered to man by various routes in extremely large amounts without deleterious effects All other antibiotics and sulfonamides, however, show a narrower difference between the toxic dose for man and the toxic dose for susceptible microorganisms These latter drugs, therefore, can be administered only in certain well defined amounts

The microorganisms susceptible to the bacteriostatic action of sulfonamides are usually the same irrespective of the type of sulfonamide derivative tested although the potency of the various drugs may differ appreciably Similarly, the untoward effects of treatment with sulfonamide derivatives tend to be the same, but the toxicity solubility, and elimination of one as compared to another may be quite different Selection of a sulfonamide as an antibacterial drug, therefore will depend upon consideration of its antimicrobial potential and its relative toxicity and absorbability from the gastrointestinal tract Sulfadiazine is the agent usually recommended in treatment of trachoma and lymphopathia venereum, largely because there has been a more extensive experience with this drug than with any other in treatment of these infections

The antimicrobial action of sulfonamides is dependent upon their ability to compete with the microorganism for para aminobenzoic acid The effect of sulfonamides is limited in the presence of pus and other tissue fluids and at low pH, and for this reason topically applied sulfonamides in trachoma have less effect than do the tetracycline drugs

The untoward reactions to sulfonamides observed in some patients are characterized by granulocytopenia, crystalluria hematuria, nephritis dermatitis, and other manifestations of hypersensitivity Granulocytopenia is the commonest reaction observed and it is important for the person receiving these drugs to be examined frequently for depression of the blood neutrophils

Penicillin is a bactericidal and bacteriostatic antibiotic produced by certain strains of the mold Penicillium, but it has also been synthesized Penicillin G (benzyl) and penicillin V (phenoxymethyl) are most active and commercially available as the potassium salt The pharmacologic action of penicillin as an antimicrobial is determined by the drug's ability to interfere with the incorporation of a nucleotide into the cell wall, resulting in cell lysis or impairment of cell multi

recommended for routine treatment Oral administration is not an acceptable means of giving penicillin in the treatment of syphilis A 6 months' follow-up examination of the patient with adequately treated early syphilis should include a serologic test If there is no appreciable decrease in titer, retreatment is probably necessary

Late latent syphilis detectable only by a positive serologic test, rarely results in neurosyphilis, but cardiovascular lesions and gummas may occur Treatment of the previously untreated patient with a positive serologic test is, therefore, mandatory The dose of penicillin and its method of administration are the same in late latent syphilis as in early syphilis, but failure of the serologic titer to return to negative does not have the same significance, and retreatment after 6 to 12 months may not be necessary

Late syphilis, associated with gummas cardiovascular lesions, paresis, optic atrophy, meningitis Charcot joints, etc, should be treated with large doses of penicillin The response to antibiotic treatment of some of these manifestations of late syphilis however, is negligible This is particularly the case in those situations accompanied by destructive changes without appreciable inflammatory reaction, as seen in tabes optic atrophy, and Charcot joints In these conditions fever therapy combined with penicillin may be desirable although not generally used at present

One million units of procaine penicillin administered daily or given every other day, for 12 to 20 injections is the preferred treatment in late syphilis Herxheimer reactions associated with fever, or precipitation of vascular accidents in syphilitic aortitis may appear within a few hours after beginning treatment of late syphilis These reactions, however, are infrequent except in paresis, in which 50 per cent of the patients may temporarily show increasing agitation and confusion after the onset of therapy

Syphilis in pregnancy should always be treated with penicillin, even if treatment had been previously given, unless the serologic test is negative The drug should be given in the first trimester of pregnancy if possible The infant born of a mother who has been treated for syphilis should be followed by serologic tests at 1 and 6 months of age

Congenital syphilis in the newborn should be treated with procaine penicillin in a dosage of 200,000 units per kilogram of body weight, or approximately 1 5 million units, given in divided doses for 8 to 10 days Interstitial keratitis and syphilitic hydrarthrosis respond poorly, if at all, to penicillin therapy

The administration of penicillin or tetracycline early in the course of experimentally produced Weil s disease is effective in controlling the infection Treatment of the naturally occurring disease in man, however, is usually of little benefit probably because recognition of the illness and onset of therapy in the human being is often deferred Nevertheless, penicillin and tetracycline are the drugs of choice in Weil s disease Penicillin may be given in a dose of 5 to 10 million units a day, and the tetracycline may be given in a dose of 2 to 4 Gm per day There is no predictable response to this therapy, and treatment should be continued for the duration of the acute illness

Leptospiral meningitis is often a self-limited form of benign 'aseptic' or lymphocytic meningitis which does not ordinarily require specific treatment Other forms of leptospirosis are also usually self limited infections

The viral and rickettsial infections are associated with intracellular parasitism Few of the antibiotics and chemotherapeutic drugs have demonstrated activity on microorganisms found within cells, and this would be expected to limit the effectiveness of these agents in treatment of viral and rickettsial diseases However, the rapidity with which tetracycline and chloramphenicol produce recovery in psittacosis lymphopathia venereum, trachoma, and the rickettsial infections suggests that these antibiotics may have the ability to penetrate cells and exert their antimicrobial action Studies of the effect of chloramphenicol upon *Rickettsia tsutsugamushi* infecting cells in tissue culture supports this suggestion by illustrating a rapid disappearance of viable organisms from the cells and a reduction in infective titer

RATIONAL BASIS FOR NEW DRUGS

It can only be hoped that in the near future drugs such as the antibiotics will be developed for treatment of virus infections The impact of antiviral agents, if as effective as antibacterial drugs, would significantly alter our concern about infectious diseases The possibility that drug resistant variants of viruses, rickettsiae, and spirochetes might appear could prove as difficult as the problem currently produced by the staphylococci It is not unlikely, however, that ways will be found to interfere with the parasitism by viruses, dependent as these organisms are upon an intracellular habitat Means of altering the susceptibility of cells to invasion by viruses could provide the means for preventing as well as treating infection If it becomes necessary to depend exclusively upon antiviral drugs, it is unlikely that prevention of infection will be possible, and such drugs may have little or no impact upon the incidence of infection Methods of increasing host resistance to viral invasion will be required to control the occurrence of the common cold, grippe, and other acute respiratory infections Acquired immunity to these commonly occurring virus infections is ordinarily of short duration and the great variety of pathogenic strains renders it almost impossible to provide much protection by the techniques of vaccination Newer concepts for the control of virus disease will most certainly have to evolve

The variability of host resistance to rickettsial infection, illustrated by relapsing disease in scrub typhus, and the inability to provide effective prophylaxis against Q fever with bacteriostatic antibiotics indicate the desirability of finding rickettsiocidal drugs It is very likely that such agents will be synthesized or uncovered but it is disappointing in the several years since the discovery of penicillin that practically no other bactericidal antibiotics with low toxicity have been produced Streptomycin and bacitracin are two of the bactericidal drugs other than penicillin, but they have limited usefulness, and their toxicity is of such magnitude as to preclude administration in large doses over long periods of time

The inability of bactericidal drugs to affect significantly the clinical course of leptospiral infections such as Weil s disease illustrates the problem presented by microbial diseases which continue to progress after reaching a certain point even though the microorganism is eradicated The future approach to this problem will necessitate efforts to understand and control the host's response to infection This is partly responsible for the high level of interest in adrenal corticosteroids in

plication Penicillin is active primarily against rapidly growing microorganisms

The amount of penicillin which can be safely administered to a human being is limited more by the cation of the salt than by the drug's toxicity One million units of potassium penicillin contains about 0 2 Gm potassium, and this dose of the cation can restrict significantly the use of penicillin in the patient with renal insufficiency Nevertheless, the most frequent untoward reactions to penicillin are attributable to drug hypersensitivity, characterized by serum sickness, fever, arthralgia, and, rarely, anaphylaxis

The three tetracycline antibiotics presently used widely are oxytetracycline (Terramycin), chlortetracycline (Aureomycin), and tetracycline (Achromycin, Steclin, Panmycin, Tetracyn, etc) These drugs are bacteriostatic and have identical antibacterial actions They are products of the molds Streptomyces and can be converted one into the other by chemical manipulation Selection of one drug is determined largely empirically, but also by their varying toxic effects

Tetracycline antibiotics affect a wide spectrum of bacteria, but their most impressive therapeutic effect has been demonstrated in the treatment of rickettsial infections, lymphopathia venereum, trachoma, and psittacosis Although commonly used, these antibiotics are not usually the preferred drugs in treatment of other microbial infections

The toxic effects of tetracycline are observed primarily in the gastrointestinal tract, producing diarrhea, nausea, and vomiting Rarely, more serious complications may arise, including staphylococcal or monilial enterocolitis and pneumonia These secondary infections in patients given tetracycline are believed to follow alteration of the normal bacterial flora by the drugs and replacement by antibiotic-resistant bacteria or fungi

Chloramphenicol is an antibiotic elaborated by *Streptomyces venezuelae* but is now produced commercially by chemical synthesis It is a bacteriostatic drug with about the same antibacterial spectrum as tetracycline, although it has a more impressive effect in salmonella and staphylococcal infections Chloramphenicol has been used widely in the treatment of rickettsial infections where it is considered the drug of choice

Chloramphenicol interferes with protein synthesis by the microorganism, and this action is probably responsible for its bacteriostatic effect The drug produces fewer gastrointestinal side effects, and secondary resistant bacterial infection in patients receiving chloramphenicol have been reported less frequently than with tetracycline Chloramphenicol has been responsible for a few serious toxic reactions characterized by aplastic anemia and death This complication restricted the use of the antibiotic for several years, but it is now being used more often. Aplastic anemia may arise from toxic suppression of the bone marrow by excessive dosage of the drug, but it has also been observed when the antibiotic was given in small doses, which is possibly attributable to a hypersensitivity reaction

The appearance of resistant mutants among microorganisms susceptible to the antibacterial action of antibiotics has not been observed with viruses, spirochetes, and rickettsiae although it is probable that such variants might develop Therefore, development of resistant organisms does not require the elaboration needed in considering the antibiotics of choice in bacterial infection

THE CHOICE OF DRUGS FOR STIMULATION OF MENTAL AND PHYSICAL ACTIVITY

Robert G Heath, M D , and

Donald D Lathrop, M D

INTRODUCTION

This discussion will be concerned with a number of compounds that are used primarily for the purpose of stimulating mental activity, some also stimulate physical activity An ideal stimulant drug would produce elevation of mood and feeling and enhance efficiency of thought without undesirable side effects At present, no such ideal preparation exists However, a number of preparations, though falling far short of this ideal goal, are employed for this purpose The stimulant drugs most extensively used over the years fall into two main categories the sympathomimetic amines and the piperidine derivatives In addition, there are less frequently used and less effective central stimulants which have been evaluated over prolonged periods Recently, the amine oxidase inhibitors have been introduced as useful central stimulants None of these compounds is free of undesirable side effects and with all there is a real question as to their effectiveness in actually fulfilling the desired goal In this respect, one must be very careful in evaluating their worth The reader will note that we devote relatively little space to some new drugs which are being widely advertised In the interest of safety, a certain amount of conservatism is indicated Although experience with the new 'antidepressant drugs is somewhat limited, there is sufficient evidence to warrant caution in prescribing any of the avalanche of these new drugs

CLINICAL APPLICATIONS

Stimulant drugs are employed in the treatment of a large number of clinical disorders Their principal, positive clinical effect is to ward off fatigue through inducing a state of wakefulness They also frequently induce euphoria Complications can and do result from this response and, in addition, undesirable physiologic side effects sometimes can occur In no instance can their effect be considered curative The degree of symptomatic improvement which they induce is greater in the treatment of some disorders than of others Their use is purely empiric and their effectiveness in all conditions is unpredictable The clinical

the treatment of infection These drugs have the capacity for altering inflammation, metabolism, and other responses to microbial invasion, even though they exert no influence upon the microorganism Further understanding of the mode of action of these hormones in infection may provide the means of controlling disease, and the antibiotics can then be used selectively for eradication of the causative microbes

SELECTED REFERENCES

Beerman, H, Schamberg, I L, Nicholas, L, and Greenberg M S Syphilis Review of the Recent Literature, A M A Arch Int Med 101: 952, 1958

Bozeman, F M, Hopps, H E, Danauskas, J X, Jackson, L B, and Smadel, J E Study on the Growth of Rickettsiae I A Tissue culture System for Quantitative Estima

Carter, A

Finland

ment of Acute Respiratory Infections and Influenza, New England J Med 247 557, 1952

Jawetz E Problems of Antimicrobial Therapy, Ann Rev Med 5 1, 1954

Kass, E H, and Finland M Adrenocortical Hormones in the Management of Infection, Ann Rev Med 8 1, 1957

Klatskin, G Leptospirosis, Yale J Biol & Med 27 243, 1955

McCrumb F R, Jr, Snyder M J, and Woodward, T E Studies on Human Infection With Pasteurella Tularensis
the Prophylaxis of Clinical Di

Meyer, K F, and Eddie, B Chemo
Trial of Tetracycline, Chlc
Chemother 5 289, 1955

Petersdorf, R G, and Bennett, I L, Jr Treatment of Mumps Orchitis With Adrenal Hormones Report of 23 Cases With Note on Hepatic Involvement in Mumps, 99 222, 1957

Smadel, J E, Adair, C V, and Gauld, R L, Aseptic meningitis, a Disease of Diverse Etiology Int Med 39 675, 1953

Smadel, J E, Leon ycetin in the Treatment of Patients Med 68 12, 1948

Tigertt, W D, and Tr A Am Physicians 69 98, 1956

Med 43 287, 1955

Bacterial Complications of Measles,

ns Occurring During Chemotherapy
sing Factors, New England J Med 251 247, 1954

Woodward, T E, and Wisseman C L Chloromycetin (Chloramphenicol), Antibiotic Monographs, No 8, New York, 1958, Medical Encyclopedia, Inc

for themselves It is in this group that the stimulant drugs are especially contra indicated The consumption of sympathomimetic amines or amine oxidase inhibitors for prolonged periods will sometimes precipitate decompensating overt psychotic symptoms in this group Patients with true psychotic depression do not obtain the desired amelioration in their mood disorder from the stimulating drugs Rather these drugs tend to produce increased agitation in his group Marsilid in some instances is an exception in this regard although it too, usually fails to induce improvement in psychotic depression A small number of cases have been re ported in which a dramatic decrease in psychotic depressive symptoms occurs fol lowing its administration

The Neuroses —Stimulant drugs are widely used in treating a number of the symptoms of neurotic patients Since their principal desirable effect is to increase productiveness through delaying onset of awareness of fatigue, these drugs produce the greatest symptomatic improvement in those patients whose predominant psy chological pattern of adaptation is such that they must perform and please in order to feel secure The groups who gain the most symptomatic benefit are, there fore the classical obsessive and the neurotic or reactive depressive patients

These over all diagnostic categories in themselves are quite broad and the establishment of a classic diagnosis is not sufficient indication for treatment with stimulant drugs Before prescribing the stimulant drugs for a neurotic patient, the physician should be somewhat familiar with the patient's psychodynamics or pat terns of adapting to life situations Reactive depressions, for example, occur for a number of reasons Most normal individuals will react to the death of a person they love very much with normal grief presenting symptoms resembling depression Stimulant drugs would be ineffective in such a situation and their prolonged usage could produce undesirable effects On the other hand, the insecure person who is depressed because he feels unloved and rejected unless performing at a very high level would gain relief from the increased production which these drugs could induce One however, must always be cognizant of the fact that inefficient or neurotic patterns must ultimately be resolved through psychotherapy The drug effects, at best, are temporary, and the pre existing faulty patterns will be present after the drug effects disappear or when tachyphylaxis develops as it does with all of these compounds For temporary alleviation of specific neurotic symp toms Dexedrine is the drug of choice Several relatively new drugs currently are used for treatment of mild and severe depression These include 2 dimethylamino ethanol tartrate (Deaner), captodiamine (Suvren), orphenadrine (Disipal) mepa zine (Pacatal) imipramine HCl (Tofranil), and the amine oxidase inhibitors—iproniazid (Marsilid) isocarboxazid (Marplan), nialamide (Niamid), β phenyl isopropyl hydrazine HCl (Catron), and phenelzine dihydrogen sulfate (Nardil) None of these compounds in the hands of the practitioner, has proved as dramati cally successful and free of side effects as hoped for on the basis of enthusiastic preliminary studies Only time and wide experience will provide us with a sober evaluation of these new compounds

Obesity —Obesity is a complicated symptom and a manifestation of multiple etiological factors Certain stimulant drugs are useful in curbing the appetite of those individuals in whom the symptom is a manifestation of a neurotic pattern They are of no value in those patients who are obese because of an underlying

syndromes for which treatment with stimulant drugs is most widely advocated and the rationale for their use in each instance will be briefly described

The Functional Psychoses—The group of functional psychoses would include predominantly schizophrenia and manic depressive psychosis Schizophrenia is not well defined and authorities in the field differ widely in their criteria for making this diagnosis All however, would agree that the majority of patients with psychosis exclusive of those with demonstrable cellular disease would fall into this category Differences exist in regard to the incidence of manic depressive psychosis Some authorities include manic depressive disorders in the category of schizophrenia There are well established clinical psychologic and physiologic data to indicate an over all impairment of physiologic and psychologic levels of awareness in psychotic patients Virtually all manifest demonstrable retardation in motor activity as determined by clinical motor tests There are impairment and fragmentation in their thought processes There are disturbances in association and affectivity The psychotics have impairment of reality testing and exhibit autism Even more fundamentally they display an inability to integrate feelings of pleasure, and their concept of themselves in the social scheme is defective

The nature of these symptoms is such as to suggest that a stimulant drug to enhance pleasurable feelings and produce an over all heightening in level of psychologic awareness is indicated However all of the popular stimulant drugs have been widely employed in the treatment of psychosis without significant effect On the contrary most of the stimulant drugs especially the sympathomimetic amines and amine oxidase inhibitors such as iproniazid have been reported to cause an exacerbation of *some* psychotic symptoms particularly overt schizophrenic symptoms i e delusions hallucinations and symptoms resulting from excitement in the manic patient It long has been known that Sodium Amytal is of some value in causing a temporary remission of certain psychotic symptoms particularly catatonia Its hypnotic effects however tend to limit its usefulness for this purpose When administered in conjunction with a stimulant drug the hypnotic effects are somewhat combated without obliteration of its temporary normalizing effect Thus there is a limited indication for the use of stimulant drugs as an adjunct to Sodium Amytal for the purpose of temporarily ameliorating psychotic symptoms in psychotic patients When used alone however, they are of no real value and, in fact there is some evidence that they are contraindicated in the treatment of this major disorder

There is a large group of patients considered by many authorities to be basically schizophrenic whose symptoms are not sufficiently severe to warrant their hospitalization They have been categorized by many persons as pseudoneurotic schizophrenics They present symptoms which resemble those of the neurotic patient but they are more disorganized than the classic neurotic patients and display fundamental symptoms of schizophrenia which are extremely difficult for the physician who is not especially trained in psychiatric diagnosis to detect Since one of the most prominent symptoms is a persisting pleasure deficiency, the doctor is apt to be tempted to prescribe stimulant drugs which can produce euphoria for this group Patients with this disorder, in an effort to overcome their deficiency are constantly searching for relief and are prone to prescribe the stimulant drugs

accurately evaluated The results of these studies suggest that the effectiveness of these compounds is minimal at best The drug of choice in the treatment of depressive reactions in the aged is Dexedrine *in low doses* *When agitation is also* present the stimulant drugs combined with a sedative or tranquilizer are more effective Metrazol and pipradrol also reportedly have been used effectively None of these compounds has *been shown to produce a specific effect, however* since there has been no statistically valid improvement in memory, orientation or general strength with any of these compounds which is over and above that noted *in control patients subjected to a good ward routine*

Alcoholism —Stimulant drugs have been used to alleviate the psychic pain of hang over in the alcoholic These drugs do not counteract or aid in the elimina *tion of alcohol in the system* but through their central stimulant effects do relieve some of the morning after effects It has been reported that the drugs will help to prevent alcoholic excess in some patients For prevention of excessive drinking they are most effective in patients who are drinking to relieve symptoms of the pain of reactive depression The rationale for their effect in this condition has been described under The Neuroses The drug of choice for reviving the un conscious drunk is methylphenidate administered intravenously For hang over effects Dexedrine or a chlorpromazine Dexedrine combination orally is recom mended The time honored remedy of caffeine in the form of coffee is likewise of merit in combating acute alcoholic effects as well as morning after ' hang over

Neurologic Disorders —These compounds have proved useful as adjuncts in the treatment of a large number of neurologic disorders

Parkinsonism —Dexedrine and pipradrol have proved of value in the treat ment of Parkinsonism in conjunction with the antispasmodic drugs Their greatest usefulness is in the relief of muscular rigidity and oculogyric crisis Dexedrine is the drug of choice

Narcolepsy —The group of stimulant drugs are the only effective medication for the relief of this symptom and results are by and large quite gratifying Quite favorable results have been reported with the use of methylphenidate, Dexedrine and recently with pipradrol Unusually large doses are required—up to thirty times the usual therapeutic level There is no way of predicting adequate dosage Because of tachyphylaxis a gradual increase in the dosage level is usually required

Spastic Disorders —Dexedrine is the first stimulant drug reported to be effec tive in the treatment of spastic disorders Recently pipradrol has been reported as effective in the relief of spasmodic torticollis blepharospasm and tics Dexedrine and pipradrol are drugs of choice

Epilepsy —Dexedrine is reported to be of value in the control of petit mal seizures in some patients The value of the stimulant drugs as adjuncts to the conventional anticonvulsant medications however, is extremely limited, and at present they are used only on rare occasions to produce increased alertness in pa tients where this is indicated

Pharmacologic Depression —Stimulant drugs have been used to combat acute depression due to overdosage of sedative and hypnotic drugs More recently they have been used in combination with sedatives and tranquilizers to prevent excessive drowsiness in patients taking these medications over prolonged periods

metabolic disorder The sympathomimetic amines, particularly Dexedrine and Preludin are the drugs of choice They are effective temporarily probably because of mild peripheral physiologic effects on the smooth musculature of the alimentary tract as well as for central stimulating or psychologic reasons The principal psychologic factor involved in overeating is a feeling of being unloved Such feelings are derived from the patient s interpersonal relationships during childhood—usually the relationship between mother and child These persons feel insecure in love relationships with others and are overly sensitive to rejection In the adaptation of the child first and closest love relationships are closely interwoven with the intake of food In the faulty adaptive pattern of the adult, intake of food becomes a substitute for love and security Patients with obesity problems are subject to reactive depression

Behavioral Problems in Children —Although the discovery that amphetamine may sometimes oroduce 'normalization" in both hyperactive and hypoactive children was made almost twenty years ago there is still no adequate explanation for this effect Nevertheless, in hyperactive and aggressively noisy children—children inclined toward antisocial acting out—as well as in quiet and withdrawn children, the stimulant drugs may exert a salubrious effect Where withdrawal is a manifestation of schizophrenia or where acting out is a manifestation of a psychopathic personality, an unfavorable result may be expected However, in the much larger group of children whose motor behavior is either markedly below or markedly above the norm, the stimulant drugs tend to normalize Present data suggest that the sympathomimetic amines, either Dexedrine or amphetamine, are the drugs of choice in the management of behavioral patterns in children However, limited data suggest that pipradrol might be equally effective

Several reports indicate that the stimulant drugs may be of value in the symptomatic treatment of enuresis in children Psychiatric studies have indicated consistently that bed wetting most frequently occurs when the child is in deep and usually dreamless sleep—occasionally it is associated with a simple, wishful dream, the commonest dream content being that he is at the toilet The rationale for use of the stimulant drugs is that through prevention of deep sleep, enuresis will not occur Since bed wetting is an emotional problem involving the parent child relationship the value of stimulant drugs is highly questionable They may help temporarily in relieving the symptoms but as in most situations the consequences of the undesirable effects of the loss of the restorative qualities of the deep sleep must be weighed against the value of the temporary amelioration of the symptom Pipradrol and Dexedrine are most commonly advocated as drugs of choice

Geriatric Problems —Virtually all groups of stimulant drugs have been advocated as useful in the management of patients with cerebral damage resulting from age i e , senility and cerebral arteriosclerosis In these patients there is actual cell damage and the rationale for the use of stimulant drugs is that they might improve the functioning of remaining cells, thereby lessening or removing decompensating behavioral symptoms Despite many rather glowing reports of the effectiveness of a number of compounds one's optimism must be guarded Recently, a number of excellent control studies have been reported where the effects of good ward management and the additional attention and enthusiasm on the part of the staff that surrounds the introduction of a new compound have been more

gesics such as aspirin and phenacetin For migraine, caffeine is synergistic [cut off] *ergot alkaloids* *Caffeine appears to constrict cerebral blood vessels and th[cut off] duce the cerebral blood flow* In hypertensive individuals the cerebrospinal [cut off] pressure may fall somewhat Dexedrine, also in combination with analgesic[cut off] been found to be useful in the treatment of tension headaches It is recomme[cut off] particularly for treatment of those patients in whom there is a prominent de[cut off] *sive component to the underlying personality*

Stimulants as an Adjunct in Psychiatric Interview—The use of stim[cut off] drugs to assist in psychiatric interview has a long and colorful history Prim[cut off] have used drugs which alter the state of consciousness in an attempt to obtain [cut off] information both from natural and supernatural sources In modern psychi[cut off] *practice the use of stimulant drugs is intended to facilitate release of repressed* [cut off] suppressed material

In hysterical amnesia the stimulant may result in immediate relief from [cut off]nesia often with a very dramatic abreaction and release of tension Stimu[cut off] drugs have the distinct advantage over the hypnotic drugs because they do [cut off] *foster postinterview drug amnesia* *Administration of stimulants may also be* [cut off]ful in the differential diagnosis of certain pyschiatric disorders In schizophr[cut off] patients, catatonic features become more intense Manic patients show an int[cut off]fication of mania and depressed patients with underlying agitated features bec[cut off] severely agitated

The drug of choice for the purpose of psychiatric interview is methamph[cut off]mine Where the blood pressure is not severely elevated (above 200 systoli[cut off] 120 diastolic) 20 mg of the drug is given intravenously in 1 ml of solution T[cut off] may be an immediate effect characterized by marked increase in the flow of spe[cut off] intensification of underlying feelings, aggravation of delusions and hallucinati[cut off] and free verbalization of these experiences *The maximum effect is usually reac*[cut off] within 15 minutes and may last for 1 or 2 hours It is often worth while [cut off] follow the use of the stimulant drug with a sedative such as Sodium Amytal [cut off] Gm) intravenously *Frequently, this sedative phase of the interview will br*[cut off] forth additional information as the patient lapses into a more relaxed state

It is usually not wise to use this procedure on outpatients, since severe e[cut off]tional reactions may ensue When possible, it should be done early in the day [cut off] that the large dose of stimulant will not interfere with the patient's ability to sle[cut off] *It is often worth while to prescribe a sedative at bedtime following this proced*[cut off]

Dexedrine and amphetamine may also be used for this purpose but in our [cut off]perience methamphetamine gives excellent results without severe side reactio[cut off] It is likely also that pipradrol and methylphenidate may be useful for this purp[cut off] but they have not received adequate trial to date

Psychologic Reaction to *Physiologic* States—The frequently encounte[cut off] problems of premenstrual tension nausea and vomiting in pregnancy, and men[cut off]pausal syndromes have been studied extensively from both the physiologic a[cut off] emotional points of view Regardless of one's orientation *there seems to be* [cut off] reason to doubt that there is an emotional component to each of these conditio[cut off] *In many persons who are predisposed to reactive depression* there is a psycholog[cut off] element of loss of love involved in these conditions In the hysterical patient t[cut off]

The management of acute depression due to overdosage of sedative and hypnotic drugs is certainly controversial There have been a large number of articles extolling the virtues of almost every conceivable kind of treatment There is a recent report containing convincing evidence that analeptics such as Metrazol, Coramine, amphetamine, and caffeine are without value and may even increase the hazard of narcosis by causing convulsions, cardiac irregularity, and vomiting If anoxia has been a prominent part of the patient s clinical course, analeptics are contra indicated Supportive management has been found to produce better results than supportive management plus analeptics in a large group of patients In milder cases of poisoning, where anoxia has not supervened, there may be some value to giving stimulant drugs Although they do not hasten the metabolism of the seda tive, they may raise the level of consciousness sufficiently to prevent aspiration and permit the patient to attend to some of his own needs Of course, the danger of adding vomiting and convulsions to the already overburdened central nervous system is involved inevitably We do not recommend a drug of choice here because we feel supportive treatment is preferred management

The use of stimulants in combination with sedatives, hypnotics, tranquilizers antihistaminics, and anesthetics is becoming ever more popular A large number of such preparations are available and the variety of combinations is limited only by the imagination of the pharmaceutical manufacturers The physician who de sires to individualize his treatment will find that Dexedrine or methamphetamine will serve admirably to counteract depression or drowsiness in most instances Occasionally, as in the treatment of upper respiratory and allergic disorders, ephed rine (25 mg, 2 or 3 times daily) will be the drug of choice to serve as a stimulant

For those who prefer proprietary preparations, we recommend selecting one that seems preferable and becoming familiar with its use rather than attempting to follow nuances of the recommendations of the manufacturers A combination of chlorpromazine and Dexedrine (Thora Dex) which is available in two dosage forms (chlorpromazine 10 mg, Dexedrine 2 mg chlorpromazine 25 mg, Dexedrine 5 mg) has been found most convenient in our hands when combined therapy is indicated There have been reports of good results with combinations of chlorpromazine or reserpine with pipradrol or methylphenidate but we have found the chlorpromazine Dexedrine combination to be more convenient for general use

Headaches—The vast majority of headache problems confronting the physi cian are of the tension type Tension headaches are a response to intrapsychic (i e faulty patterns based on faulty learning) as well as extrapsychic stresses (i e, realistic external problems) Not uncommonly, there is an element of de pression involved Furthermore, the sufferer frequently finds that tension head aches interfere with his ability to perform his regular duties, which leads to ex asperation and frequently to intensification of the head pains Likewise, in mi graine headaches there is an undeniable association between the emotional state and the occurrence of attacks The headaches associated with hypertension are due primarily to the increase in spinal fluid pressure but in some instances also to the emotional state of the individual

The drug of choice in the symptomatic treatment of headaches of these types is caffeine For tension headaches, it is usually given in comb nation with anal

The observation that usage of drugs which increase the level of amines in the body sometimes leads to psychotic behavior is most provocative Employment of the amphetamine preparations on rare occasions will do this Also there are reports of overt psychotic symptoms being brought on in some patients through use of the amine oxidase inhibitor, iproniazid With this compound it can be presumed that amine levels in the body are increased by virtue of the inhibition of the enzyme which normally would metabolize amines These observations suggest that disturbances in amine metabolism may be an important factor in endogenous psychosis The present stimulant drugs have their greatest worth when an extended but self limited period of wakefulness is necessary They are also of considerable value in the treatment of narcolepsy In both situations, the temporary sympathomimetic effect can serve a useful purpose Allowance must be made for an adequate period of convalescence to combat the accumulative fatigue in these circumstances

The prescribing of current popular stimulant drugs presents a great temptation to the physician The drugs produce an immediate effect which is apt to give the physician a false feeling of gratification that he is able to work quick magic with his patients It is necessary for the physician to be aware that these effects at best are temporary and that present drugs do not provide an adequate substitute or short cut for thorough work up and the time consuming process of gaining an understanding of his patient which is essential to resolve the basic underlying pathology

THE SEVERAL DRUGS

Sympathomimetic Amines—The first major group of chemicals to be considered are the sympathomimetic amines Of these, four are important clinically amphetamine dextroamphetamine, methamphetamine, and mephentermine Although ephedrine historically is important for its central and peripheral stimulating properties it rarely is used now solely for these effects The four derivatives listed above possess the desirable central stimulating properties of ephedrine with much less tendency to produce the undesirable peripheral stimulant effects

Amphetamine is a racemic compound while dextroamphetamine is the dextro rotary form The latter is about twice as potent a central stimulant as the former Methamphetamine is a more potent cortical stimulant than amphetamine its central action being more rapid in onset and more prolonged It is slightly less active on the peripheral system Mephentermine is a mild central stimulant and has a potent pressor effect The mechanism of central stimulating action of these drugs is not known They are known to inhibit amine oxidase and this is believed to be the basis for their sympathomimetic action

Amine Oxidase Inhibitors—Because of enthusiastic early reports of the effectiveness of iproniazid as an antidepressant' a number of compounds in this category have been marketed recently Since there are many and varied types of compounds which can inhibit amine oxidase it is likely that we will see even more compounds with this function appearing in the future Efforts are directed toward finding an amine oxidase inhibitor with high antidepressant activity and low or absent toxicity Although antidepressant compounds are classified as amine oxidase inhibitors it is a highly speculative assumption that a causal rela

No drug has been found to be invariably effective in the treatment of these conditions However, there is adequate rationale for the use of stimulant drugs in their management The drugs of choice are Dexedrine, amphetamine and methamphetamine They are most commonly used in combination with a sedative, such as amobarbital an analgesic such as aspirin or a tranquilizer, such as chlorpromazine Again the physician will do well to familiarize himself with the combination of these drugs which is most appealing to him Excellent results can be obtained with any of these compounds if they are given at the appropriate time in adequate dosages

Premenstrual Tension —For premenstrual tension it is recommended that the drug be started 1 to 2 days before the expected onset of the symptoms Dexedrine is the drug of choice

Nausea and Vomiting of Pregnancy —In the management of nausea and vomiting of pregnancy, Dexedrine in combination with chlorpromazine is often effective The antiemetic effect of chlorpromazine together with the antidepressant effect of Dexedrine often results in relief of this symptom Use of combinations of chlorpromazine and pipradrol have also been reported but appear to possess no particular advantage over the chlorpromazine Dexedrine compound

Menopausal Syndrome -- Similarly in the menopausal syndrome where the symptoms are mild and especially when mild depressive symptoms predominate the use of Dexedrine amphetamine or methamphetamine alone or in combination with sedatives and tranquilizers sometimes produces gratifying results

GENERAL PHARMACOLOGIC CONSIDERATIONS

The need for an ideal stimulant drug is greatest in the field of psychiatry In the field of mental and nervous disorders the greatest single need is for a compound which will induce a basic feeling of true pleasure On the basis of clinical observations as well as from physiologic studies a compound that fulfills this function is likely to be effective in the treatment of the psychoses Some existing compounds including sedatives as well as stimulants do produce a type of euphoria This however is a quite different phenomenon from the inducement of a real pleasure feeling and existing compounds are not effective in alleviating psychoses An ideal pleasure inducing compound should be effective in alleviating emergency emotional responses such as fear and rage and logically therefore would improve an individual s rational thought processes

The stimulant drugs which are considered in this presentation are stimulants only in rather specific areas Most are primarily sympathomimetic and those which are preferred and most widely used possess the quality of stimulating central nervous system activity with a lesser degree of peripheral autonomic effect Their principal central effect is to increase wakefulness which they do quite adequately This however is not a wholly desirable effect It results in delaying but not eliminating fatigue Thus the letdown effects after discontinuation of the medication are quite marked because of cumulative fatigue One cannot prolong the inevitable fatigue by continuing to take these medications since tachyphylaxis develops and the drug gradually loses its effect Prolonged usage because of accumulative excessive fatigue will often lead to muddled inefficient thinking and poor performance

Practically nothing is known of the *mechanism of action of these drugs*, and we may only speculate that since they have in common the piperidine ring this may be the pharmacologic common denominator Pipradrol has been demon strated to intensify electrical activity in subcortical structures

Pentylenetetrazol —This drug a tetrazol derivative, known also as Metrazol and Cardiazol affects primarily the rostral brain stem but has a *lesser cortical* stimulant effect

Caffeine —Caffeine, a member of the xanthine family, stimulates the cortex and brain stem in addition to its familiar cardiovascular effects

A DESIGN FOR THE USE OF DRUGS FOR STIMULATION

Sympathomimetic Amines —For general use, Dexedrine or methamphetamine may be started at 2 5 mg, 2 or 3 times a day Most patients will tolerate a start ing dose of 5 mg, 2 or 3 times a day The time of administration of the drug is determined by the effects desired and by the appearance of side effects In most cases of depression *a dose should be taken on arising in the morning when depres* sion tends to be most severe In the same patients, a late afternoon dose may aggravate insomnia, if this occurs, a morning and noon dose only should be given In obesity, when appetite control is desired, medication given 30 to 60 minutes before meals is most satisfactory Sustained release preparations give the physician the greatest advantage in appetite control since the patient can take a capsule early in the morning and then forget his appetite instead of forgetting to take his medication for the remainder of the day

If the desired effect is not obtained in 3 to 5 days at 5 mg, 3 times a day, increase one dose by 2 5 mg Repeat this procedure until maximum benefit or intolerable side effects occur When appetite suppression is not desired give with or after meals If insomnia occurs, give the afternoon dose earlier or decrease it

The dose of amphetamine required to produce equivalent central stimulation *is about twice that of Dexedrine However, the same initial regimen may be used* in order to avoid undue side effects Since all of these drugs are tachyphylactic smaller initial doses and gradual increase will produce few severe side reactions This also will make occasional readjustment of dosage necessary

These drugs are convenient to use because they are rapid in onset of action *(15 to 30 minutes) and brief in duration of action* (4 to 6 hours)

Higher doses than might be expected will be tolerated by children with be havioral disorders The regular starting regimen outlined above for adults may *be used In narcolepsy, tremendous doses may* be *required* ranging *up to 30 times* the average dose required for treatment of other conditions

Amine Oxidase Inhibitors —Isocarboxazid (Marplan) like its precursor iproniazid (Marsilid), may be given in a single daily dosage or divided dosage Start Marplan at 30 mg daily and level off to 10 to 20 mg daily in 3 to 4 weeks

Iproniazid (Marsilid) *should be given in a single dose* *In mild* depression begin with 50 mg a day and reduce to the minimum effective level as soon as possible (2 to 4 weeks on the average) In severe depression or in regressed psychosis the initial dosage is 150 mg daily until improvement occurs and then the dosage should be reduced to the minimum effective level (25 to 30 mg daily)

tionship exists between inhibition of amine oxidase and mood elevation Such a relationship has never been clearly demonstrated and it indeed, may be a paradoxical side effect of some of these compounds which results in mood elevation in some patients Further investigation into the mode of action of these compounds is indicated

These drugs cause an accumulation of serotonin and norepinephrine and inhibit detoxification of various drugs by the liver barbiturates amphetamines and aminopyrines) Complications and side effects include psychotic reaction orthostatic hypotension edema hypochromic anemia constipation dizziness diaphoresis impotence delay in micturition insomnia restlessness tremulousness dry mouth etc Hepatocellular necrosis resulting in jaundice and rarely, in death has been reported with Marsilid This is an imposing list of complications but it is worthy of note that severe complications are relatively uncommon and usually accompany high dosage levels and prolonged administration Unquestionably these drugs have produced some dramatic results Before their usefulness can be finally judged however further evaluation is required When they are used it must be under careful medical supervision

Iproniazid (Marsilid) a potent amine oxidase inhibitor causes an accumulation of serotonin and norepinephrine and inhibits detoxification of various drugs by the liver (barbiturates amphetamines and aminopyrines) Complications and side effects include psychotic reaction hypotension edema hypochromic anemia vitamin B_6 deficiency syndrome constipation dizziness diaphoresis and hepatocellular necrosis resulting in jaundice and rarely in death This is an imposing list of complications, but it is worthy of note that the incidence of fatal complications is extremely rare and the others listed usually follow administration of the drug in high doses for prolonged periods On the positive side this drug recently has been heralded as a real pharmacologic advancement in so far as the treatment of depressive symptoms is concerned Before its effects can be finally judged this compound requires further evaluation and when it is employed it demands thorough familiarity and conscientious medical supervision

Imipramine HCl —Tofranil is structurally related to the phenothiazines It is speculated that it exerts an antidepressant effect by virtue of sensitization of central adrenergic synapses This remains to be proved

Side effects include orthostatic hypotension dryness of mouth tachycardia constipation and occasionally visual disturbances

As with the other new drugs caution and close surveillance are required when this compound is employed

Deanol —Deanol (Deaner) is believed to be a precursor to acetylcholine It is speculated that its particular stimulant action in the central nervous system is related to the ease of penetration of deanol base across the blood brain barrier Because of its physiologic action it is low in toxicity Accumulated clinical evidence however suggests that this preparation is quite ineffective

Piperidine Derivatives —Two chemically related compounds which have become popular recently as mental and physical stimulants are piperidine derivatives These drugs which have had wide clinical trial, are pipradrol (Meratran) and methylphenidate HCl (Ritalin)

dose may be increased or decreased depending upon results in the individual Or doses of 60 to 90 mg a day are not uncommon In fact, as with the other drug dosage may be safely increased until desired results are obtained or side effects be come intolerable When the drug is given intravenously, 0 2 mg per pound is recommended starting dose

Other Drugs—

CAFFEINE —Caffeine is often given intramuscularly for acute conditions, 0 Gm being the usual dose Oral medication is used commonly in combination witl other drugs or in beverages, the average dose is 0 15 to 0 5 Gm

PENTYLENETETRAZOL —Pentylenetetrazol (Metrazol, Cardiazol) when givei orally is prescribed in tablets containing 0 1 or 0 2 Gm A reasonable starting dos is 0 2 Gm, 3 times daily When given to elderly patients, the drug may be expectec not to produce significant effects in less than 90 days However, it is often possibl to increase the dose by 0 1 Gm a day after about 2 weeks if the patient does no appear ashen, tremulous, or excited When used intravenously for activation o epileptogenic foci a 10 per cent solution is injected slowly Normal subjects acti vate, i e, become anxious and tremulous after an average of 3 5 ml, and the epi leptic patients show electroencephalographic changes at an average of 2 3 ml

IMIPRAMINE —Imipramine (Tofranil) may be started intramuscularly in hos pitalized patients at 100 mg daily in divided doses This may be increased in increments of 25 mg daily up to 300 mg per day if necessary to obtain the desired response Dosage for outpatients is 200 mg daily Maintenance dosage varies from 50 mg to 150 mg daily

Complications and side effects are similar to those described under amine oxidase inhibitors Glaucoma is also a contraindication

DEANOL —Deanol (Deaner) may be used for mild depressions Begin with 50 mg daily in single dosage Side effects include headache, constipation over stimulation and insomnia These are relieved by reduction of dosage or temporary suspension of treatment Effects are seen in 1 to 3 weeks at which time a minimum maintenance dosage of 10 to 25 mg daily may be instituted

RATIONAL BASIS FOR THE DEVELOPMENT OF NEW STIMULANT DRUGS

As emphasized throughout this discussion, the sympathomimetic effect as produced by presently popular stimulant drugs, is a nonspecific action in the treat ment of a number of clinical entities As evidenced by recent research, it is be coming more apparent that psychotic behavior which is numerically the greatest indication for a satisfactory stimulant is a manifestation of a faulty metabolic proc ess The essential requirement for a drug to meet the needs in this area is that it will satisfactorily correct the endogenous defect This will require considerable research into the nature of the disorder The compound that fulfills this need will be perhaps better classified as corrective rather than 'stimulant'

SELECTED REFERENCES

Allin, T G, Jr, and Pogge R C The Use of Azacyclonol and Pipradrol in General Prac tice Internat. Record Med & G P Clin 169 222, 1956

Vitamin B complex containing pyridoxine should be given simultaneously The blood pressure should be checked frequently and the dosage reduced or the drug stopped if hypotension becomes severe Warn patients to avoid postural hypotension. Edema can be controlled with diuretics Watch obese patients for weight gain as this drug often stimulates appetite dramatically

Phenelzine dihydrogen sulfate Nardil is started at 15 mg 3 times a day with meals Look for a response in 2 to 5 days but maintain dosage until maximum response is gained usually less than 6 weeks Maintenance dosage should be around 15 mg

β Phenylisopropyl hydrazine HCl Catron is started at 12 mg daily in the morning for 1 to 2 weeks When a response occurs reduce to minimal maintenance level, about 3 mg daily

Nialamide (Niamid) may be started at 75 mg daily in single or divided dosage After 7 to 10 days raise or lower the dosage depending upon response Maintenance dosage is 12 5 to 25 mg daily

With all of these drugs the use of minimal maintenance dose is essential to reduce side effects Often a regime of one half tablet on even days and a whole tablet on odd days will be sufficient

Patients must be warned about orthostatic hypotension If hypotension becomes severe stop the drug Edema can be controlled with diuretics Obese patients must be watched for weight gain as this often accompanies administration of these medications *Serial liver function tests have been recommended but* appear to be of little value since altered liver function has not correlated with the occurrence of complications Jaundice may subside with discontinuance of the drug and has subsided with continuance of the drug Continued drug administration in the presence of jaundice however is not recommended

Contraindications to these drugs are impaired hepatic or renal function epilepsy, and electroconvulsive therapy They should be used with great caution with sedatives, hypnotics narcotics alcohol and local and general anesthetics

Piperidine Derivatives —

PIPRADROL.—Pipradrol (Meratran) should be started generally at 1 mg, 2 or 3 times a day If the patient tolerates this well and the desired results are not obtained within a week, increase to 2 5 mg, 2 or 3 times a day There are reports of initial cryptic weight loss of a few pounds as well as other side effects Weight usually will tend to stabilize and many side effects decrease or disappear by the end of a week Some persons are capable of tolerating higher dosage without side effects and some seemingly have a higher threshold for the effects of the medication Therefore if dosage up to 2 5 mg, 3 times a day, does not produce satisfactory results it is worth while before discarding this drug as ineffective to increase 2 5 mg a day each week until the desired results are obtained or undesirable side effects occur In spastic disorders and in narcolepsy, very large doses (5 to 30 times the usual dose) may be required

METHYLPHENIDATE —Methylphenidate (Ritalin) may be given in 5, 10, or 20 mg tablets An average oral starting dose is 10 mg, 2 or 4 times a day Observe the patient for several days then adjust the dosage by adding 5 or 10 mg a day Some patients will require only 5 mg, 2 or 4 times a day, and the

THE CHOICE OF A STIMULANT TO VITAL MEDULLARY CENTERS

McKeen Cattell, Ph D , M D

INTRODUCTION

The rational use of therapeutic agents for the stimulation of medullary functions *requires consideration, not* only of the limitations of the drugs presently available for clinical use, but perhaps more important, of the therapeutic effects to be expected from such symptomatic therapy Here consideration will be limited to drugs which stimulate two medullary centers namely, the respiratory center and the vasomotor center The choice of a drug to produce emesis, which involves another function centered in the medulla is discussed elsewhere

CLINICAL APPLICATIONS

Man and other warm blooded animals are endowed with effective regulatory mechanisms for respiratory and vasomotor control, two functions which are essential to life It is important from the standpoint of achieving rational drug therapy to consider the status of these regulatory mechanisms in the clinical conditions in which the objective is to restore a failing respiration or peripheral circulation Here we are concerned with the contribution which could reasonably be expected from drugs *which stimulate the medullary centers controlling these functions*

Respiratory Stimulants —In general drugs which stimulate respiration under normal conditions are not effective when the center is depressed to an extent reducing external respiration below the needs of the body This is presumably due at least in part to the fact that under such circumstances carbon dioxide, the *natural stimulus to the respiratory center, accumulates in the body* Carbon dioxide is the most effective stimulant known and it is therefore not surprising that under these circumstances drugs may fail to call forth a further response It can be shown experimentally in an animal severely depressed that respiratory stimulants produce no effect short of convulsive doses

Vasomotor Stimulants —Drugs *which stimulate the vasomotor center* cause a rise in the blood pressure and are generally classed as circulatory stimulants It is worth while to consider what one can hope to accomplish by the use of circulatory stimulants Excluding those drugs which improve cardiac function we have to

Andren, H E Treatment of Depression With Meratran and Electroshock, Dis Nerv System 16 275, 1955
Barrabee, P, Wingate, J H, Phillips, B D, and Greenblatt, M Effects of L-Glutavite Compared with Metrazol and Vitamins on Aged Female Psychotic Patients, Postgrad Med 19 485, 1956
Bradley, C Benzedrine and Dexedrine in the Treatment of Children's Behavior Disorders, Pediatrics 5 24, 1950

Natenshon, A L Clinical Evaluation of Ritalin, Dis Nerv System 17 392, 1956
Newman, H W, and Newman, E J Failure of Dexedrine and Caffeine as Practical Antagonists of the Depressant Effect of Ethyl Alcohol in Man, Quart J Alcohol 17 406, 1956
Rosner, B S, Fierman, L B, and Kramer, J F Clinical Evaluation of Meratran and Frenquel on a Chronic Psychotic Population, Am J Psychiat 113 993, 1957
Rudolf, G de M The Treatment of Depression With Methylamphetamine, J Ment Sc 102 358 1956
Symposium on the Biochemical and Clinical Aspects of Marsilid and Other Monoamine Oxidase Inhibitors, J Clin & Exper Psychopath 19 (suppl to No 2) 1958
Tennent, J J Experiences With Metrazol in Psychoses With Cerebral Arteriosclerosis, Psychiatric Quart 30 249, 1956

tral stimulants results from respiratory depression The secondary respiratory depression limits the use of stimulants to acute emergencies and precludes their *administration* over a long period of time

DESIGN FOR USE OF DRUGS FOR MEDULLARY STIMULATION

In view of the pharmacologic and physiologic considerations which have been briefly reviewed in this chapter, it *is apparent that medullary stimulants have but* very limited therapeutic application

Artificial Respiration —The most direct approach for the correction of an in adequate respiratory exchange is to apply artificial respiration When this is done, the addition of carbon dioxide to the inspired air serves to maintain a high level in the blood and tissues and thus provides an effective respiratory stimulus and, in case of hyperventilation, prevents the carbon dioxide tension from falling to un physiologic levels This is accomplished by employing a mixture of 7 per cent CO_2 and 93 per cent O_2

Caffeine —Probably the most widely used and generally useful central nervous *system stimulant is caffeine In addition* to its action on the higher centers it has a definite effect on the respiratory center and probably to a slight extent on the vasoconstrictor center Whatever the cause of the central depression, if not too severe, caffeine can be expected to temporarily improve the general alertness of a depressed patient Such symptomatic therapy cannot be regarded as lifesaving but the use of caffeine is favored by its relative freedom from side effects However since too vigorous treatment can readily induce a further depression the single dose of caffeine should not exceed 1 Gm, and, if it is to be repeated, the second dose should be given only after the elapse of several hours

Other Medullary Stimulants —Other medullary stimulants, such as picrotoxin and pentylenetetrazol, may be useful in antagonizing the depressant effects of seda tive drugs, such as the barbiturates Specific blocking agents, such as levallorphan (Lorfan) and nalorphine (Nalline), provide the most effective treatment for re spiratory depression caused by morphine and certain other opiates These com pounds are not medullary stimulants and their use is considered in Chapter 12

At the present time we have no drugs which are employed clinically for stimu lation of the vasomotor center The same ends are accomplished when indicated by a *variety of drugs* which belong to the group of sympathomimetic agents and which cause constriction by a direct action on the blood vessels These are dis cussed in Chapters 26 and 27 on vasoconstrictor and vasodilator drugs

RATIONAL BASIS FOR NEW DRUGS TO COUNTERACT DEPRESSION OF MEDULLARY FUNCTION

Since, at best, medullary stimulants cannot do more than relieve a symptom consequent to some bodily disorder or to the direct action of a toxic agent, this therapeutic approach has extremely limited applications It is doubtful that even an ideal medullary stimulant could be expected to contribute appreciably to the therapy of respiratory or vasomotor *depression Rather, therapy should be directed* toward the removal of the cause of the depression In this direction progress is

consider only those agents which bring about a constriction of the peripheral vessels by either a direct or a central action and thus cause an increase in the arterial pressure When the pressure falls from any cause, the sensory endings in the carotid sinus are stimulated and a reflex vasoconstriction ensues Even in an advanced state of shock or peripheral vascular failure, this mechanism is operative Thus the vasomotor center continues to function normally during advanced failure with very low blood pressure, at which time the arterioles are maximally constricted

Effective stimulants of the vasoconstrictor center are not available, but even if they were it is doubtful that they would be useful under these conditions There is the further consideration that whenever arteriolar constriction occurs the blood flow through the organ supplied is decreased Although this results in a rise in blood pressure and an increased flow of blood to the heart and brain which may improve temporarily the apparent condition of the patient, it does so at the expense of worsening the fundamental difficulty—an inadequate supply of blood to the tissues In other words, the blood pressure is raised at the expense of blood flow

Sympathomimetic Amines —The physiologic considerations described above are also pertinent to the rational use of peripherally acting vasoconstrictors It is important to note that they do not necessarily constitute a contraindication to the use of vasoconstrictor agents to combat an *acute* drop in blood pressure as, for example that resulting from influences mediated through the central nervous system or from the blocking of the sympathetic innervation during spinal anesthesia It has for example been shown experimentally in dogs that norepinephrine added to a dextrose saline infusion during the first hour after an otherwise fatal hemorrhage greatly increased the number of animals surviving the period and increased survival time after replacing the blood To tide over a temporary period of low blood pressure before the advent of peripheral vascular failure a number of sympathomimetic amines are available such as phenylephrine (Neo Synephrine) and norepinephrine (levarterenol Levophed)

GENERAL PHARMACOLOGIC CONSIDERATIONS

The actions of respiratory and vasomotor stimulants are not confined to the medulla but extend in varying degree to all parts of the central nervous system Indeed it is probable that their value depends in part upon the general improvement which may be induced in central functions and the reflection of this stimulant effect on the medulla Ephedrine probably acts through this mechanism

The effectiveness of medullary stimulants is determined by the state of the centers the functions of which it is desired to improve As indicated above, if the circulation or respiration is depressed by other than central mechanisms, little can be expected from the use of drugs On the other hand, if the condition is a result of some toxic agent acting on the center, such as a barbiturate, and the depression is not too great, improvement may result from the use of such drugs as picrotoxin and pentylenetetrazol (Metrazol, Cardiazol)

It is well to bear in mind two unfortunate pharmacologic properties of central stimulants, which limit the amount which can be administered In large doses they cause convulsions which must of course be avoided, and, further, initial stimulation is followed by depression The fatal outcome from excessive doses of cen

THE CHOICE OF DRUGS FOR THE RELIEF OF PAIN

John J Bonica, M D

INTRODUCTION

The usual introductory remarks justifying a writing are hardly necessary in presenting a discussion on the management of pain, for reflection emphasizes that this task has been for centuries, and still remains, a difficult clinical problem which confronts every practitioner of the healing arts In fact, the existence of pain and possibilities for its management probably constitute the most ancient reasons for the existence of the physician, for pain is as old as mankind As the records of every race are examined, one finds testimonials to the omnipresence of pain, and as long as pain has existed there have been efforts to find means of controlling it Its management has for all times taxed the diagnostic acumen and therapeutic skill of physicians

The monumental achievements of medicine during the last quarter century have made possible prevention or elimination of a great deal of suffering The great strides taken by all branches of surgery and anesthesia have made it possible to remove the cause of the pain or to interrupt its pathways in circumstances which previously precluded surgical intervention Moreover, the development of many systemic analgesics, local and general anesthetics, and other agents has provided the physician with a huge arsenal filled with pain relieving remedies these, together with the great progress made in psychosomatic medicine and psychiatry, physiatry, roentgen therapy, orthopedics, and all other medical services, have greatly enhanced the effectiveness of the physician s efforts in relieving pain Yet despite these advances, the management of pain remains one of the most difficult and often vexing phases of medical practice, not only because it is the leading symptom of many diseases and therefore constitutes one of the most frequent reasons for patients seeking counsel of their physician, but also because often it is a complex and distressing problem It is obvious, therefore, that the proper management of pain constitutes (from the patient's standpoint at least) the most important obligation, one of the main objectives, and the crowning achievement of every physician

THE NATURE OF PAIN

In order to understand some of the principles in managing patients with pain and the proper therapeutic application of various drugs, some insight into the

being made in the synthesis of compounds which block the action of toxic agents A better understanding of the factors contributing to failure of nerve centers in disease would contribute to the solution of this problem

SELECTED REFERENCES

Bard, Philip editor Medical Physiology, St Louis 1956, The C V Mosby Co

Dale, H H, and Evans, C L Effects on the Circulation of Changes in the Carbon Dioxide Content of the Blood, J Physiol 56 125, 1922

Drill, V A, editor Pharmacology in Medicine, New York, 1954 McGraw Hill Book Co, Inc

Eckenhoff, J E, Schmidt C F, Dripps R D, and Kety, S S A Status Report on Analeptics J A M A 139 790, 1949

Gilmore, J P Effectiveness of Levarterenol During Hemorrhagic Hypotension, Am J Physiol 195 473, 1958

Goodman L, and Gilman, A Pharmacological Basis of Therapeutics, New York, 1956,

Liljestrand [illegible] 2 623 1951

Watts, J [illegible] Poisoning Com

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THE NATURE OF PAIN

In order to understand some of the principles in managing patients with pain and the proper therapeutic application of various drugs some insight into the

nature of pain is essential. The scope of this book and limitation of space permit only mention of the most important aspects. A more detailed dissertation may be found in other books by the author and others.

Although people know what is meant by the word pain, many have great difficulty in defining it. This is so because pain is a highly personal affair entirely subjective in nature and a complex physiopsychologic phenomenon which almost defies enquiry. Aristotle considered pain as a 'quale' or passion of the soul, a state of feeling, the antithetic experience from pleasure, and the epitome of unpleasantness, together with pleasure, these were the main normal driving forces that guided man's actions. This concept was accepted until the middle of the nineteenth century, when scientists began to consider pain as a sensation. Presently a number of authorities believe pain to be composed of two parts: the perception of pain and the reaction to pain. Perception of pain is a neurophysiologic process which has special structural, functional, and perceptional properties and is accomplished by means of relatively simple and primitive neural receptive and conductive mechanisms. It is measurable and constant, although it can be modified by drugs and psychic factors and completely obviated by interruption of its pathways by chemical (nerve block) or surgical means.

On the other hand, the reaction to pain is a complex physiopsychologic process which involves the cognitive functions of the individual. It represents the emotional and physiologic expressions resulting from the perception of pain: it is what the individual feels, thinks, and does about the pain he perceives. The pattern of reaction depends, in part, upon what sensation means to the individual in the light of his past life experience, his attitude toward it: his judgment, mood, emotional status, and will, the state of his nervous system and the various cerebral processes, the presence or absence of anxiety, and many other factors. Obviously, the reaction to pain is different for each individual; indeed, with the passing of time and the accumulation of life experience, it is never exactly the same for an individual from one time to another.

Although this artificial dichotomy of the pain experience has proved useful in studying and understanding it, it is doubtful that there is such a thing as a pure sensation of pain separate and distinct from the influence of reaction. For one thing, the processing of the psychic reaction to the original stimulus probably begins before awareness of the sensation has been achieved. There are many who firmly believe that the essential part of pain is awareness and no other sensation or experience can be termed pain unless it is felt as such. The obvious conclusion is that the "quale" or feeling state, i.e., the patient's complaints, and his physical and mental responses are the manifestations of the reactions and are the most relevant aspect of the pain experience—certainly to the patient. This is one of the most important and fundamental facts about pain: it must be accepted with its full implications if one is to be successful in managing patients with intractable pain. The importance of the reaction or the affective component of pain from a therapeutic standpoint will be emphasized further in the discussion of the addictive analgesics, the hypnotics, and the placebo.

The origin of pain may be a stimulus in the somatic or visceral structures of the body and acting on the peripheral part of the nervous system, or it may be in the central nervous system and projected to a distant part of the body, as is found

in the pain of the thalamic syndrome, in the painful aura of sensory epileptiform seizures, or in the conversion type of pain in hysteria Here we are primarily concerned with pain of peripheral origin, because it is this type which is most frequently encountered by the practitioner and the one which is manageable with drugs

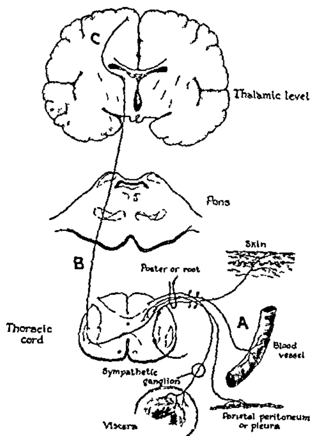


Fig 5—A simplified schematic diagram which illustrates the three relays of nervous elements involved in the conduction of pain from the periphery to the brain *A* peripheral, *B* connecting, and *C* central neurons It should be noted that the neuron conducting pain from the viscera passes through the central nervous system in association with sympathetic fibers and will thus pass through the prevertebral and paravertebral sympathetic ganglionic chain However these fibers are constituents of the spinal nerves having their cell bodies in the posterior root ganglion and entering the central nervous system via the posterior root as do sensory fibers from other structures The secondary neurons form the spinothalamic tract, which in this diagram is represented by one neuron for the sake of clarity The central neurons take origin in the thalamus wherein they synapse with the secondary neuron and end in the cerebral cortex (From Bonica, J J Management of Pain, Philadelphia 1953, Lea & Febiger)

The nervous pathways for pain arising in the somatic and visceral structures may be said to be organized into three distinct units or relays the first relay, the peripheral sensory neurons, the second relay, the connector (internuncial) neurons, and the third relay, the central sensory neurons as depicted in Fig 5

Although pain sensation is probably also integrated in the mesencephalon and thalamus, the cortex is the highest level of such integration which results in the

nature of pain is essential The scope of this book and limitation of space permit only mention of the most important aspects A more detailed dissertation may be found in other books by the author and others

Although people know what is meant by the word pain, many have great difficulty in defining it This is so because pain is a highly personal affair entirely subjective in nature and a complex physiopsychologic phenomenon which almost defies enquiry Aristotle considered pain as a 'quale' or passion of the soul, a state of feeling, the antithetic experience from pleasure, and the epitome of unpleasantness together with pleasure, these were the main normal driving forces that guided man's actions This concept was accepted until the middle of the nineteenth century, when scientists began to consider pain as a sensation Presently a number of authorities believe pain to be composed of two parts the perception of pain and the reaction to pain Perception of pain is a neurophysiologic process which has special structural, functional, and perceptional properties and is accomplished by means of relatively simple and primitive neural receptive and conductive mechanisms It is measurable and constant, although it can be modified by drugs and psychic factors and completely obviated by interruption of its pathways by chemical (nerve block) or surgical means

On the other hand, the reaction to pain is a complex physiopsychologic process which involves the cognitive functions of the individual It represents the emotional and physiologic expressions resulting from the perception of pain, it is what the individual feels thinks, and does about the pain he perceives The pattern of reaction depends, in part, upon what sensation means to the individual in the light of his past life experience, his attitude toward it his judgment, mood, emotional status, and will, the state of his nervous system and the various cerebral processes, the presence or absence of anxiety, and many other factors Obviously, the reaction to pain is different for each individual, indeed, with the passing of time and the accumulation of life experience, it is never exactly the same for an individual from one time to another

Although this artificial dichotomy of the pain experience has proved useful in studying and understanding it, it is doubtful that there is such a thing as a pure sensation of pain separate and distinct from the influence of reaction For one thing, the processing of the psychic reaction to the original stimulus probably begins before awareness of the sensation has been achieved There are many who firmly believe that the essential part of pain is awareness and no other sensation or experience can be termed pain unless it is felt as such The obvious conclusion is that the 'quale" or feeling state, i e, the patient's complaints, and his physical and mental responses are the manifestations of the reactions and are the most relevant aspect of the pain experience—certainly to the patient This is one of the most important and fundamental facts about pain, it must be accepted with its full implications if one is to be successful in managing patients with intractable pain The importance of the reaction or the affective component of pain from a therapeutic standpoint will be emphasized further in the discussion of the addictive analgesics, the hypnotics, and the placebo

The origin of pain may be a stimulus in the somatic or visceral structures of the body and acting on the peripheral part of the nervous system, or it may be in the central nervous system and projected to a distant part of the body, as is found

or widespread disease Moreover, the intensity of pain is not generally increased by the summation of neural impulses from noxious stimulation at different sites Patients with long standing pain do not get accustomed to it, but rather seem to become more 'sensitive' to it and suffer more with the passing of time Protracted pain no matter whether moderate or severe, produces physical and psychologic depletions which vary widely between individuals and may be evidence of basic personality differences

General debility, malnutrition, fatigue, anxiety, and mental turmoil lower the reaction threshold still more so that the pain is more severe and more difficult to treat Lack of sleep is particularly important in this respect Patients with chronic suffering have a gradual but complete alteration in their attitude to their environment Consequently, they have no other interest and the pain in fact becomes a consuming problem which completely dominates their lives In such cases interruption of pain pathways with consequent complete abolition of pain perception cannot be expected to solve the problem entirely In many instances the problem is much more complicated and necessitates a long term application of psychotherapeutic and rehabilitative measures as well

METHODS OF PAIN CONTROL

From what has been said, it is apparent that there is need for orientation regarding the totally functioning human being in the evaluation of such a complex phenomenon as pain *It is essential that the physician make an intelligent appraisal* of the patient with pain in order to make a diagnosis of the over all disease and that he understand the underlying pain mechanisms and formulate a systematic plan for relief that will provide the best results

From the standpoint of approaches to treatment it is desirable to differentiate that which is primarily structural primarily physiologic, and primarily psychologic When there is a significant psychic factor, as in many psychophysiologic disorders, or when there is pain related to personality factors but without demonstrable physiologic changes, the treatment of the psychologic problem becomes paramount In these cases it is essential that one treat the underlying psychophysiologic condition and the fundamental methods of psychiatric management must be considered A discussion of psychiatric technique is beyond the scope of this chapter, but the importance of this method in managing patients with severe intractable pain cannot be overemphasized An excellent dissertation on this subject has been written by Ripley

Now let us focus our attention on patients with pain of structural etiology and altered physiologic function without structural change Although psychologic support is very useful in helping these patients, the main treatment is directed to the elimination of the primary disease This may be accomplished medically by means of drugs (antibiotics, antispasmodics, spasmolytics [curare] vasodilators vasoconstrictors, etc), by surgical extirpation of the lesion, or by physical methods (roentgen therapy, physical therapy, etc) In such patients with pain due to self limiting medical diseases or due to disorders which indicate surgical extirpation the solution of the pain problem is usually clear cut and relatively simple However, in patients with protracted pain, the cause or mechanism of which cannot be

normal apperception of pain The very complex intercommunications between the postcentral gyrus, where are concentrated the thalamocortical projections and other parts of the cortex results in an intimate functional relationship among these various parts This relationship makes possible the mobilization of all sorts of associations based upon past experience and judgments so that the individual is able to evaluate the particular sensation It is here that the sensation is converted into a painful experience by incredibly complex physiopsychologic mechanisms sensation becomes perception percepts are further elaborated into concepts concepts cluster together to form ideas and ideational constellations, and all of these events undergo mnemonic engramatization i e, formation of memory traces which in part form the basis of the reaction to the sensation Here occurs the formulation of the individual reactions to the perception or appreciation of pain Moreover, it is here that the appreciation of the stimulus is further modified by the state of activity of other cortical centers particularly those located in the frontal lobe, so that the appreciation is aggravated or inhibited

Some Characteristics of Pain

Noxious stimulation produces pain which differs in its characteristics according to the structures involved The characteristics of pain of special interest to the clinician include quality intensity, duration and extension Noxious stimulation of superficial somatic structures (skin subcutaneous tissues) produces pain which has a sharp quality is well localized and is felt quickly Pain induced by noxious stimuli applied to the deep soma (fascia, periosteum tendon, subcutaneous tissue) is duller and more diffuse than cutaneous pain Pain resulting from application of pain stimuli to viscera is usually described as a dull aching sickening discomfort which the patient has difficulty in localizing because it is diffuse and is not so rapidly perceived

There are several other important characteristics of pain which must be kept in mind Pain is rarely constant in intensity for a protracted period The brief severe lancinating pain of trigeminal neuralgia is an extreme example the pain of carcinomatosis is notoriously waxing and waning In addition to intrinsic mechanical and chemical factors which may cause the pain to become more or less severe environmental changes may be important Pain is generally worse at night because the distractions and mood modifying effects of the day s activities are not present when the patient is quiet in bed he becomes preoccupied with his condition

There is no constant necessary or proportionate relationship between the perception of pain and the reaction to that perception The obvious inference of great clinical importance is that the intensity of pain or amount of suffering experienced by the patient is independent of the size of the lesion Perhaps the paramount factor in determining the intensity of pain and suffering is the significance of its source If there is no worry or other distressing implication regarding its source pain is comparatively well tolerated

Another characteristic of pain is that when two or more sources of pain stimuli exist coincidentally perception of pain is monopolized by the most intense a point of great clinical significance when treating patients with metastatic lesions

When the decision has been made, it is important to inform the patient and, if circumstances warrant, also his family about the plan of treatment A general outline of the procedures, the effects that may be expected, and what may be ac complished must be explained in detail

Since persistent pain exacts a heavy price in the form of physical and mental depletions, it is most important to provide complete relief at the earliest possible date Although the systemic analgesics are most frequently used in treating severe, intractable pain, it must be realized that they seldom completely relieve pain, but merely make it more tolerable For this reason it is important to consider the early use of some method to interrupt pain pathways before tolerance and addic tion to analgesics develop

All patients who experience severe, chronic pain require psychologic support and moral encouragement The first positive step in relief of intractable suffering occurs when a physician manifests his responsibility and willingness to properly discharge his obligation for the care of the patient In addition to the benefits made possible by modern science, the physician should bring to the patient a sympathetic understanding, kindness, cheerfulness, and reassurance Since patients are quick to sense an attitude of defeatism or lack of interest, the physician should do all he can to instill into the patient confidence and a sense of security based upon the conviction that all will be done to relieve his suffering The general practitioner, by virtue of the proper rapport and confidence which he has cultivated in the patient, is best qualified to carry out this phase of management

Measures to support the patient physically are also essential, not only to com pensate for physiologic depletions, but also because malnourished patients do not tolerate pain as well as those in good physical condition The diet should be high in proteins, vitamins, and calories If anemia is present in spite of proper therapy, transfusions should be given In addition, good hygiene and competent nursing care together with rest and sufficient sleep are necessary

PRINCIPLES OF THE CONTROL OF THE SEVERAL VARIETIES OF PAIN

Neuralgias

Neuralgia is a broad descriptive term that is frequently indiscriminately em ployed for any pain Its use should be restricted to the literal connotation—nerve pain that is, pain with a segmental or peripheral nerve distribution It is usually a symptomatic expression of an inflammatory, mechanical, circulatory, toxic, de generative or neopastic neuropathy, radiculopathy, or myelopathy It may be the first and only manifestation of the pathologic process, although in many instances it is accompanied by hyperesthesia and hyperalgesia or diminution of sensations and other neurologic symptomatology, which at first may be of such minimal degree as to escape the attention of all but the most careful ex aminer The chronicity of the pain and its persistence until the cause is re moved make it mandatory that these cases be studied carefully and the cause ascertained and removed, if possible Occasionally the neuralgia constitutes the entire clinical syndrome without any apparent etiologic basis or structural changes In such instances it is necessary to direct the entire treatment to the elimination of

ascertained or eliminated, the problem is often very difficult from a therapeutic, as well as from a diagnostic, standpoint Such cases require a well planned attack that is based upon fundamental principles which must be followed if good results are to be achieved

In such instances the diagnosis and localization of the source of pain usually require a thorough detailed examination and a correct interpretation of medical neurologic, radiologic and laboratory data It becomes immediately apparent that proper management of such patients requires a great deal of time and effort, more than some practitioners are willing to spend, but unless the physician is willing to devote the necessary time to the problem, he cannot hope to achieve optimal results In fact, he may do more harm than good

In taking the history of the pain three phases or periods should be considered onset course and present status The location and distribution the quality, the intensity or severity and the duration of the first pain should be ascertained The characteristics of the pain at the time of examination should be determined The patient should be asked how these pains compare with those experienced at the onset and during the course of the disease The patient should be asked what circumstances or conditions have aggravated or relieved the pain and what effect emotional disturbances, movement of the part, and other activities have had on the severity, quality, and distribution of the pain What has been done and what drugs have been taken to relieve the pain and what have been the effects of these? What time of day is the pain least? What postures have relieved or aggravated the pain? In the event that associated sensory, motor, or autonomic disturbances are still present, these should be investigated

After a diagnosis has been made and the mechanism of pain is determined, it is essential to map out carefully the best course of treatment, i e, the use of procedures which are most likely to produce optimal and certain results In determining what procedure or procedures are to be used it is necessary to consider many factors The cause of the pain its site, type and mechanism its intensity, and its probable duration must be taken into account In addition, it is essential to consider the nature of the disease causing the pain and the age of the patient, his physical and mental status his life expectancy, and his obligations to his family and the community In deciding the form of treatment of pain, the methods which are locally available and practical under the circumstances must frequently be considered however, the physician should not hesitate to recommend a form of pain control available elsewhere if it is clearly superior to the methods available locally In case of doubt it is advisable to explain the advantages disadvantages and limitation of each of the methods and to let the patient and his family make the decision In special circumstances it is necessary to consider the reactions of the family toward the problem The physician has the obligation of selecting a method or methods most likely to produce results

Frequently, management of the pain problem requires application of several therapeutic methods There has been as yet relatively little clinical exploitation of a multiphasic approach to pain control by applying several well chosen combinations of therapeutic methods, each specific for certain desired effects This is usually much more effective and far more satisfactory than alteration of the reaction with addictive analgesics

The myofascial pain syndrome with trigger mechanisms constitutes one of the most common causes of disability of the shoulder girdle, low back, neck, and lower extremity in people over the age of 30 years These conditions are best treated by ethyl chloride spray or infiltration of the trigger area Nonaddictive analgesics alone or in combination with small doses of sedatives or even mild nar cotic analgesics may be used in conjunction with the injection therapy and physical therapy which are necessary for cure The same form of treatment should be employed in the management of simple sprains, fractures tendinitis, tenosynovitis, and other minor musculoskeletal disorders Whenever these conditions become chronic and are associated with persistent pain, the continuous use of addictive analgesics should be avoided

Pain Due to Peripheral Vascular Insufficiency

Peripheral circulatory insufficiency is often accompanied by pain, the severity of which depends on the degree of insufficiency and duration of its onset and mech anism of the pain Sudden obstruction of a major artery frequently produces severe ischemic pain which requires large doses of narcotic analgesics administered intravenously or intramuscularly A still better method of management is the use of continuous epidural block which if properly executed, not only provides com plete relief of pain but also produces sympathetic interruption The latter effect may relieve the spasm of the collateral arteries that frequently accompanies such disorders as traumatic segmentary vasospasm, embolism thrombosis laceration and other affections of the peripheral arterial tree

Pain associated with such chronic vasospastic disorders as Raynaud s disease, postfrostbite syndrome postpoliomyelitis syndrome and acrocyanosis is best man aged by avoiding conditions which aggravate the spasm In addition it may be necessary to employ nonaddictive analgesics and small doses of sedatives and tran quilizing agents in order to eliminate psychic factors which invariably aggravate the vasospasm If these conservative measures fail to provide relief, sympathec tomy should be considered It again should be stressed that addictive analgesics should be avoided in these patients The same comments may be made concern ing the management of obstructive diseases such as arteriosclerosis and thrombo angiitis obliterans [See Chapter 27 for the use of drugs in vasospastic disease Ed]

Headache and Other Head Pains

Headache and other pains in the region of the head and neck may be due to a great number of intracranial extracranial, systemic, and psychosomatic disorders Mild transient headaches are rarely a cause of concern and can be adequately man aged with acetylsalicylic acid Chronic periodically recurrent headaches, on the other hand are usually on the basis of emotional tension anxiety, resentment and other psychologic disturbances which produce autonomic and somatic end organ discharges resulting in vascular distention and dilatation and sustained excessive contraction of skeletal muscles of the head and neck Similar mechanisms proba bly play a significant role in the production of the migraine syndrome and the mi graine variants Obviously in all of these psychosomatic disorders treatment must

the pain This should be done early before the occurrence of physical and mental defects consequent to the pain, and it is best accomplished by interruption of pain pathways by either chemical or surgical means As previously stated, addictive analgesics should be avoided and their use limited to the control of severe acute pain for a short period of time

Reflex Sympathetic Dystrophies

The reflex sympathetic dystrophies a group of seemingly unrelated disorders which appear to be similar in etiology, in clinical manifestation, and in response to therapy are characterized by excessive, unduly prolonged pain, vasomotor dis turbances delayed functional recovery, and trophic changes Apparently, trauma or infection stimulates and injures nerve fibers and thus produces an irritative nerve lesion which serves as a chronic focus that constantly bombards the spinal cord with an abnormal number of noxious impulses and tends to initiate and perpetuate the so-called vicious circle

The extremely severe burning pain and hyperalgesia of major causalgia are rarely relieved by even large doses of narcotic analgesics but are completely eliminated by interruption of the sympathetic nerves to the part The extremely severe burning pain and hyperalgesia characteristic of major causalgia are rarely relieved by even large doses of narcotic analgesics but are completely eliminated by interruption of the sympathetic nerves to the part In view of the fact that without sympathetic interruption the pain persists, it is best to avoid continuous use of narcotic analgesics and to proceed with sympathetic interruption as early as possible The same applies to postamputation pain, including pain in the phantom limb, a complicated problem which requires intensive psychotherapy and neurosurgical management If drugs must be used, small doses of sedatives and tranquilizing agents can be prescribed

The so called minor reflex dystrophies which include Sudek's atrophy, minor causalgia, and the shoulder hand syndrome, among many others are often accom panied by dull, aching or burning pain which is persistent and may be of moderate severity Although nonaddictive and addictive analgesics may provide relief, re gional sympathetic block is preferable because it interrupts the vicious circle and thereby frequently effects a cure Analgesics may be employed to control the pain during the interval between the nerve blocks

Pain of Musculoskeletal Origin

Pain caused by disorders of ligaments, joints, muscles, tendons, fascia, bones, and other mesodermal structures is usually a symptomatic manifestation of an infectious, traumatic, degenerative, or neoplastic process Obviously, management varies according to the etiologic basis Infectious disorders require anti infective and/or anti inflammatory agents In addition, it may be necessary to employ radiation therapy and even surgical drainage Since pain of mesodermal origin responds particularly well to acetylsalicylic acid and other nonaddictive agents these drugs should be tried alone or in combination with small doses of narcotic analgesics Severe acute pain may require intramuscular or intravenous adminis tration of a narcotic analgesic, or even the infiltration of a local anesthetic agent

Although the management of chronic pain with analgesic drugs is discussed on page 236 the intractable pain of cancer deserves *special mention* *The treatment* of such pain revolves about two main methods of approach removal of the cause by decreasing the size of the tumor or completely eliminating it, and the control of the pain itself with systemic analgesics, neurosurgical means, or nerve blocks Regardless of which of these methods is to be used, it is essential to realize the great importance of *psychologic and physiologic support to these patients* *In* no other disease is the patient's need for moral encouragement, sympathetic understanding, cheerfulness, reassurance, and encouragement so great Cancer pain is often unbearable because hope, understanding, and personal interest have been withheld from the patient by the physician or nursing attendants

In cases of incurable cancer it is well recognized that several different methods which directly influence the malignant growth can be used to control the pain These include palliative operation, radiation therapy, castration, and the administration of sex hormones, nitrogen mustard, radioactive compounds, and other specific antitumor therapeutic agents Hypophysectomy, or total adrenalectomy, frequently effects recession of some metastatic lesions and subsidence of the pain The relief of pain accompanying these procedures is often dramatic and represents a great gain in time and courage When the afore mentioned measures prove totally or partially ineffective or not feasible, it is necessary to control pain symptomatically The principal means are general analgesics, neurosurgical operations, and analgesic blocks The proper uses of nonaddictive and addictive analgesics, sedatives, hypnotics, and placebos in the management of chronic pain, including pain due to cancer, are discussed elsewhere in this chapter It needs emphasis, however, that the practice of some physicians to 'snow the patient under because the end is inevitable' denotes a lack of understanding of the problem Because it is very difficult to estimate the length of life in individual cases, such an attitude may be productive of an unnecessarily premature tolerance, and, consequently, the patient may not obtain adequate relief in the later stages even with massive doses of drugs This method should be reserved for those patients who are so debilitated that nerve blocks or neurosurgery are contraindicated and for those who have such a short time to live that these procedures are inadvisable

Although a detailed discussion of neurosurgical and nerve block procedures for the treatment of intractable cancer pain is outside the scope of this book, it needs to be stressed that patients with severe, chronic intractable pain should be provided the benefit of complete relief by temporary or permanent interruption of pain pathways If the patient is still in fairly good health, peripheral neurotomy, spinothalamic tractotomy (chordotomy), or sensory rhizotomy should be carried out In patients with very severe pain not controlled by any other means, even prefrontal lobotomy may be considered On the other hand, in patients whose physical condition contraindicates operation, nerve blocks should be tried When properly applied, they serve as an excellent substitute for the operation and provide greater relief than systemic analgesics Frequently it is necessary to combine the use of nerve blocks with small doses of addictive analgesic, sedatives and other systemic drugs Such a combination provides a greater degree of relief of pain than when systemic drugs are used alone

be directed primarily toward eliminating the underlying psychologic disturbance with psychotherapy In addition, sedative and tranquilizing drugs may be of great value Acetylsalicylic acid and other nonaddictive analgesics may be employed occasionally if headache is moderately severe Narcotic analgesics should be avoided at all costs, not only because of the chronicity of these conditions, but also because the psychologic deficiencies of these patients make them particularly vulnerable to development of habituation

Headaches due to organic disorders require thorough investigation and the elimination of the cause In addition to the use of nonaddictive analgesics post traumatic headache may be relieved by injection of painful scars and the associated *spastic muscle*

Pain of Visceral Origin

Disorders of the thoracic viscera often cause pain in the chest region, which frequently requires the use of analgesic agents Mild angina pectoris can be ade quately controlled with limitation of activity and nitroglycerin drugs Severe in tractable angina pectoris may require more radical management in the form of analgesic blocks or better still sympathectomy or rhizotomy The pain associated with acute myocardial infarction can usually be adequately controlled with nar cotic analgesics In the presence of very severe pain it is advisable to administer the drug intravenously or intramuscularly in small divided doses until the patient obtains adequate relief

It is well appreciated by all clinicians that narcotic analgesics must be used with caution in patients with acute abdomen so as not to obscure diagnosis On the other hand once the diagnosis has been made pending more definitive treatment it is essential that the patient be provided relief of pain The severe often ex cruciating pain of acute pancreatitis biliary colic, and renal colic deserves special mention The combination of intravenously administered narcotic analgesics with spasmolytic agents is usually effective in providing complete and prompt relief of pain

Chronic painful conditions such as chronic pancreatitis irritable colon syn drome so called idiopathic nephralgia and postcholecystectomy syndrome require careful management Because of the chronicity of these conditions it is essential to avoid the narcotic analgesics

Pain of Malignancy

This brief discussion on the management of cancer pain has been deferred until the last in order to emphasize its great importance Although cancer may not be painful at its onset in many instances it eventually gives rise to pain that be comes progressively severe finally developing into relentless suffering that causes physiologic as well as psychologic deterioration Notwithstanding the hopeless prognosis of such cases, the pain problem deserves an intelligent appraisal and a systematic plan for relief, which will conserve the patient s physical, mental and moral resources and his social usefulness as long as possible The deplorable atti tude of defeatism and therapeutic inactivity found in some quarters must be abandoned and replaced by courageous aggressiveness tempered by sane judgment

salts or esters of salicylic acid and salicylate esters of organic acids, exemplified by sodium salicylate, methyl salicylate, salicylsalicylic acid, acetylsalicylic acid (aspirin), salicylamide (Salicim, Salrin, Liquiprin), and phenetsal (Salophen), *respectively* The para aminophenols of interest are acetanilid (Antifebrin), acetophenetidin (phenacetin) acetaminophen (Apamide, Tempra), the pyrazolons with analgesic activity include *antipyrine (phenazone)*, *aminopyrine (Pyramidon)*, phenylbutazone (Butazolidin), and dipyrone (Novaldin)

The widespread use of these agents during the past century attests to their effectiveness in relieving mild pain Today acetylsalicylic acid is used more frequently for the relief of mild pain than all other drugs combined Certainly there is no other field in which commercial drug exploitation is so extensive as in the manufacture and unrestricted "over the counter' sale of this group of drugs Although they are much less potent analgesics than the opiates and opioids, they possess the significant advantages in that they do not produce tolerance or addiction

Clinical Applications—The chief application of these drugs is for the control *of mild pain and discomfort arising from integumental structures, such as cephalalgias*, arthralgias, neuralgias, and myalgias Some of these drugs are also effective in the treatment of rheumatic disorders Administered alone they are ineffective *in controlling moderate or severe pain or in managing pain arising from smooth* muscle spasm such as occurs in visceral disorders The nature of the limited and selective action is not understood

Acetylsalicylic acid (aspirin) and sodium salicylate are the best nonaddictive analgesic agents to use because they not only are effective but are less toxic than the para aminophenols

Recently acetylsalicylic acid and salicylsalicylic acid have been combined in tablet form to provide prompt and longer lasting effect This combination is said to be especially useful as a nighttime analgesic for mild chronic pain, such as occurs in arthritis Acetophenetidin is the best substitute to use in patients who are allergic to the salicylates or for some other reason cannot tolerate them It is considerably less toxic than its congener, acetanilid The pyrazolons are inherent with risk of such severe toxic reactions as to make their use unjustified

Pharmacologic Considerations—Since the pharmacologic details of the antiarthritic *drugs are considered in* Chapter 32 only those effects which are pertinent to the present discussion will be mentioned here Because these effects of the various drugs in this group are similar, they will be dealt with together

Mechanism of Analgesia—*The exact mechanism by which these drugs* alleviate pain is not known, but it is thought that they exert a selective depressant action on the pain perception apparatus in the central nervous system, probably at thalamic levels Laboratory studies and *clinical observations indicate that they* raise the pain perception threshold but have no effect upon the reaction phase of pain That the site of action may not be cortical is further suggested by the fact that analgesic doses of these drugs cause no *mental disturbance or changes in mood* or in modalities of sensations other than pain Although some individuals claim to experience a mild sedative and hypnotic effect, this is certainly not the rule and may be either a placebo effect or may be the result of *relief from pain in an individual* who is fatigued and has lost sleep consequent to the pain

ANALGESICS

The most commonly employed method in managing pain involves the systemic administration of analgesics Analgesics, by definition, include the drugs which through their action on the nervous system reduce or abolish suffering from pain without producing unconsciousness This may be brought about in several ways (1) by interfering with conduction of noxious impulses or abnormal motor responses by direct action on the peripheral nerves, (2) by interfering with conduction of noxious impulses in the neuraxis, (3) by changing the attitude or mood of the patient to pain, by promoting freedom from anxiety, mild euphoria, or feeling of well being or by inducing apathy to the painful experience, (4) by producing sedative and soporific effects, (5) by producing a combination of two or more of these effects

Close analysis reveals that analgesics comprise several heterogeneous groups of drugs which act on various parts of the physiopsychologic system concerned with pain These include (1) those which have their effect on the central nervous system, as, for example, the opiates and (2) those which exert a local action on the pain conduction system at the site of injection, as exemplified by the local anesthetics Since it is not customary to include the local anesthetics when considering analgesics these are discussed separately in Chapter 13

Selection of the Analgesic.—In selecting the type of analgesic to be used, the quality and intensity of pain are the most important considerations Mild pain can be adequately controlled with nonaddictive analgesics Opiates and "opioids" should be postponed until the weaker drugs prove ineffective Notwithstanding laboratory evidence that no combinations of drugs have greater pain threshold raising effect than their most effective component alone, clinically the value of combinations of drugs to provide a summated or potentiated therapeutic effect has been appreciated for many years The exact mechanisms for potentiation are not clear It is frequently valuable to administer a combination of drugs which produce the same result by entirely different mechanisms This is particularly important in treating pain which is often a complex response to a number of physiologic and psychologic derangements

Dosage —It may be generally stated that with this group of drugs it is especially important to adhere to the old maxim in medicine that one should always seek and use the minimal *effective* dose This requires good clinical judgment, especially when dealing with pain, the most subjective of all symptoms From what has been said concerning variation in reaction to pain it is apparent that there will be considerable differences in requirements between individuals and in the same individual at different times This is especially important when administering drugs, exemplified by the opiates, which have their predominant effect on the reaction phase of pain Since pain is an antagonist to the depressant and other undesirable effects of drugs, the more closely the dose meets the requirements, the lower the frequencies and severity of such reactions

Nonaddictive Analgesics

The drugs comprising this group include the salicylates, para aminophenols and pyrazolons Derivatives of salicylic acid of value in pain control consist of

vertigo, weakness, and anginal pain Severe cases exhibit vascular collapse an respiratory depression Chronic poisoning, which occasionally follows regular con tinuous ingestion, is more common and more difficult to diagnose

Pyrazolons Toxicity of pyrazolons resembles that of para aminophenols ex cept that cyanosis and methemoglobinemia are not characteristic, the group als may produce agranulocytosis Sensitivity to aminopyrine *is often manifested* b herpetic eruptions around the lips and by angioneurotic edema, whereas antipyrin causes dermatitis medicamentosa Because of the serious nature of these undesir able effects these drugs should not be used as analgesics

Phenylbutazone (Butazolidin), which is also a pyrazolon, is an effective anal gesic in acute arthritis, bursitis, gout, and other acute musculoskeletal disorders Because of toxicity from prolonged use it is not indicated in patients with such chronic disorders as osteoarthritis, osteoporosis, and other chronic arthritides More than a third of the patients experience undesirable effects such as edema, gastro-intestinal distress, rash, and vertigo Instances of severe toxic reaction consisting of agranulocytosis, thrombocytopenia, hypertension hepatitis, and leukemia have been reported

[Dipyrone (Methampyrone, Narone, Novaldin) is another of the series and it may be assumed with the same toxic and therapeutic potentials Ed]

Design for the Use of Nonaddictive Analgesics

The most significant recent observation concerning these drugs is that they are as effective in doses of 0 6 Gm as in much larger doses Larger doses pro *long the analgesic action but do not afford any greater relief Therefore, sustained* relief of pain obtained with a small dose repeated at frequent intervals is better

The optimal analgesic dose of acetylsalicylic acid (aspirin) when used alone *is 0 3 to 0 6 Gm, and this may be repeated every 2 to 3 hours for* several doses Because it is sparingly soluble in water, has many chemical incompatibilities, is unstable in watery solutions, and has a nauseating taste, it is best to take it in the *solid dry tablet form* Sodium bicarbonate hastens the absorption of aspirin and neutralizes increased amounts of hydrochloric acid produced as a result of local stimulation by the aspirin Therefore, in patients who already have gastric dis tress, it may be advisable to use sodium bicarbonate or enteric coated tablets of aspirin

Acetophenetidin is also administered in doses of 0 3 to 0 6 Gm The optimal dose of acetanilid is 0 2 Gm, and that of antipyrine (phenazone) and aminopyrine (Pyramidon) 0 3 to 0 6 Gm If these doses are ineffective, larger amounts do not give any more relief Medication with any of these drugs over a period of days is not advisable unless there are intermittent periods during which analgesic drugs from other chemical classes are substituted

Rational Basis for New Nonaddictive Drugs

There is a serious need for a more potent nonaddictive systemic analgesic drug Such a drug should produce specific interruption somewhere in the pain perception apparatus in the same fashion that muscle relaxants interrupt skeletal

OTHER EFFECTS —In addition to their analgesic effects these drugs lower body temperature by action on the central nervous system, probably by raising the "thermostat" of the heat regulating center of the hypothalamus to a higher level Heat production is not inhibited, but heat dissipation is increased This effect is not seen in individuals with normal temperature, but only in febrile patients

The salicylates increase urinary excretion of uric acid In doses in the range used in the treatment of rheumatic fever they frequently produce a primary hyper ventilation and changes in the pH and electrolyte pattern of the blood They also may produce epigastric distress, nausea, vomiting, and even gastric ulceration with consequent hemorrhage In analgesic doses these drugs have little or no effect on the other bodily functions

ABSORPTION AND EXCRETION —The salicylates, para aminophenols, and pyrazolons used to control pain are readily and chiefly absorbed from the upper intestinal tract Absorption also occurs from the stomach (particularly if the pH is low) and through any mucous membranes These drugs are rapidly hydrolyzed in the plasma and their metabolites excreted, or they are excreted as conjugation products of sulfuric or glycuronic acid

TOXIC REACTIONS —

The Salicylates Salicylate poisoning is a particularly serious problem in children especially those under 2 years of age, because of the profound physiologic alteration it produces, which may even lead to death It either results from accidental ingestion of large amounts of the drug by the child, or is due to misguided therapeutic efforts of the parents, often upon the advice of the physician In very large doses the salicylates produce mild toxic symptoms collectively known as salicylism which consists of headache, dizziness tinnitus, impaired hearing, dimness of vision mental confusion sweating, thirst nausea vomiting diarrhea, and increased respiratory and pulse rates With toxic doses these progress to dyspnea, restlessness incoherent speech excitement, mania, hallucinations, and delirium Recovery usually is prompt if the drug is withdrawn Poisoning with excessive doses may progress to stupor coma and death due to cardiovascular collapse and respiratory failure This is discussed in Chapter 41

Painless bleeding from the gastrointestinal tract may occur following the prolonged use of aspirin This is particularly apt to occur in patients with peptic ulcers during the winter seasons when upper respiratory infections are treated with aspirin Idiosyncrasy to salicylates is not rare and is usually manifested by skin rashes and anaphylactoid reaction Sensitivity to these drugs occurs more frequently in patients with asthma and allergy

[There is no sound evidence that Calurin (calcium acetylsalicylate urea) has any advantages over aspirin Ed]

Para aminophenols Toxic reactions to acetanilid, acetophenetidin and the others are not uncommon because these drugs are found in many "headache powders" which are sold without a prescription and, therefore, are subject to misuse The toxicity usually comes from the ingestion of large amounts over a long period of time Overdosage results in acute poisoning, characterized by formation of methemoglobin and sulfhemoglobin, which cause the skin, mucous membranes, and fingernails to develop a cyanotic color Symptoms encountered are dyspnea,

ADDICTIVE (NARCOTIC) ANALGESICS

This section deals with the pharmacology, indications, complications, and *clinical use of* potent systemic pain relieving drugs which have as one of their inherent characteristics the potential for inducing addiction Although it has long been the custom to refer to these as *narcotics there is a trend to* use the more specific term "addictive analgesics" In the discussion that follows these two terms will be used interchangeably

Only those addictive analgesics that have been proved effective by extensive clinical trial will be discussed These comprise three major classes (1) the opiates, which are natural alkaloids of opium and include Pantopon, morphine, and codeine, (2) the synthetic opiate derivatives which include dihydromorphinone (Dilaudid) heroin (diacetylmorphine), hydroxydihydromorphinone (Numorphan) and methyldihydromorphinone (metopon), and (3) a heterogeneous group of synthetic compounds which, though dissimilar in chemical structure, have actions which are similar to the opiates The last group was formerly collectively known as synthetic opiate like compounds' *Recently the simpler term 'opioids' has* been adopted in lieu of the afore mentioned unwieldy phrase These include meperidine (Demerol), methadone (Dolophine), alphaprodine (Nisentil), and levorphan (Levo Dromoran) In addition brief mention will be made of some promising newer synthetic analgesics which have been given limited clinical trial

Clinical Applications

Opium has been employed for the relief of pain since ancient times, and throughout the ages it has been the most widely employed drug for this purpose Records of its use can be found in the Babylonian clay tablets, in the Ebers Papyrus, and in the writings of the Greeks, Romans, and almost every great historian and poet *This is a long story that is heroic in terms of alleviation of human suffering* and pain Almost three centuries ago Sydenham wrote, "Among the remedies which has pleased Almighty God to give to man to relieve his suffering, none is so universal and so efficacious as opium" Osler frequently referred to morphine as God s own medicine' Today these statements applied to the entire group of narcotics would find endorsement by most clinicians because properly administered they are of great benefit to the patient

Field of Usefulness —The addictive analgesics are capable of relieving or modifying any type of pain, except extremely severe, lancinating pains of trigeminal neuralgia tabes dorsalis, and of *certain other lesions of the* central nervous system They are of particular value to control acute, transient pain consequent to accidental or surgical trauma burns visceral disease, and musculoskeletal disorders Coronary occlusion acute pancreatitis, and biliary or renal colic are often accompanied by severe pain which requires administration of potent addictive analgesics

Acute vascular occlusion is an outstanding indication for narcotics, regardless

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rather than antagonistic Severe pains associated

muscle function or ganglionic blocking agents affect autonomic nervous system functions Such a drug might produce its block in the peripheral relay by depressing nerve function or it might interfere with synaptic transmission within the neuraxis

In order to be proved practical, such a drug should permit control of the degree of interruption as obtains with muscle relaxants, with maximal therapeutic dose it should provide complete interruption of pain perception Moreover, it should provide controllability of duration of block Obviously one of the most important qualities would be lack of undesirable side effects

A drug producing interruption of pain perception specifically could be employed in patients with pain that had a relatively small affective component It could also be used in the same manner that the nonaddictive analgesics presently available are used, in combination with a barbiturate or other hypnotic in patients who had a marked emotional factor

Dextro Propoxyphene (Darvon) —A new synthetic analgesic, dextro propoxyphene, shows promise of fulfilling some of the aforementioned requisites for nonaddictive drugs A number of studies indicate that this agent has the same analgesic potency as codeine without addictive liabilities and with significantly less incidence of side effects

Pharmacologic Considerations —Dextro propoxyphene has a chemical structure which is different from that of all other analgesics, although resembling methadone, and is a bitter white crystalline material which is readily soluble in water

The analgesic potency of dextro propoxyphene appears to be the same as codeine The number of aforementioned clinical trials have shown that propoxyphene given in 30 to 60 mg doses provided analgesia which was similar in all respects to the same doses of codeine These studies, which were carried out in patients with chronic diseases accompanied by mild to moderate pain, showed both drugs produced measurable relief of pain for 6 hours or more Darvon produced prompt analgesia following oral administration

Unlike other analgesic agents, propoxyphene has no antidiarrheal, antitussive, or antipyretic effects Prolonged administration of propoxyphene in patients with chronic pain failed to produce any adverse effects on liver or kidney function, blood elements, or on the gastrointestinal tract Moreover, no loss of analgesic activity which would indicate development of tolerance and no euphoria were observed, and, when the drug was discontinued, none of the patients developed symptoms suggesting physical dependence The addicting liability of dextro propoxyphene has also been extensively studied in patients who were addicts or former addicts, and the evidence indicates that the drug has little or none On the basis of these findings the drug has been classified as a nonaddictive analgesic agent and does not come under the preview of the Federal narcotic law

Absorption and Excretion —The drug is absorbed readily after oral as well as parenteral administration and is apparently detoxified in the liver and eliminated by the kidney

[Ethoheptazine (Zactane), a meperidine congener, is another new analgesic which is sold in combination with aspirin under the trade name of Zactirin, about which too little is known to make a definitive statement at this time Ed]

Effect on Pain Perception The second most important action of morphine and other analgesics is their interference with conduction of pain, thus raising the threshold for pain perception The focus of such action is unquestionably within the neuraxis, most probably in the diencephalon (thalamus) and in the cerebrum There is some evidence which suggests that morphine may depress afterdischarge in the closed internuncial chains between frontal lobes and diencephalon, and in this manner interferes with reverberating activity essential for the pain experience Clinical evidence that morphine has a significant impeding action on the conduction of nervous impulses that give rise to the pain is available from studies on the use of these agents as supplements to general anesthesia These studies indicate that the administration of morphine, Demerol or other analgesics before or during the administration of anesthesia significantly reduces the amount of anesthetic necessary to produce surgical anesthesia Since the patient is of course unconscious, this action cannot be on the reaction phase, therefore the conclusion that the drug interferes with conduction of the noxious impulses is not unreasonable This phase of the analgesic action of the morphine and other narcotics operates most efficiently when the drug is given before the painful stimulus is applied

Parameters of Analgesic Action —The analgesic action of morphine is highly selective, and frequently pain may be relieved with small therapeutic doses without obtundation of other modalities of sensation and with little lethargy, alteration of mentation, or respiratory depression Even when large doses are properly administered to relieve severe pain, most of the physiologic and psychologic effects are of a mild degree, because pain and the consequent increased irritability antagonize these effects Moreover, there is a mutual antagonism between pain and the analgesic action of the opiates Pain perception threshold raising action of these drugs as well as other observable effects, can be reduced or completely neutralized by pain if the pain precedes or occurs early (during the first 90 minutes) in the course of the action of the opiates Moreover, a continuous stimulus has a greater neutralizing effect on the threshold raising action of these drugs when the pain occurs just before the administration of the drug or soon after it is given On the other hand, when a painful stimulus is applied after critical period of 90 minutes, which is the peak of pain perception threshold raising action, the perception of pain is much less acute

Other Central Nervous System Effects —

Respiration Morphine depresses the respiratory center directly, the degree of depression being proportional to the dose This effect is discernible with small doses insufficient to produce sleep or disturb consciousness There is first a decrease in rate with a compensatory increase in the tidal exchange, but the latter is gradually diminished so that eventually, with large doses there is a decrease in respiratory minute volume

Emesis The vomiting center is stimulated by morphine and its congeners so that about 10 minutes after injection the subject may begin to experience nausea Due to the psychologic effects, however, the vomiting is not associated with the usual unpleasant emotional reactions

Other Effects Morphine decreases olfactory and auditory acuity, cutaneous perception, and the sense of muscular tone Morphine also depresses the cough

ciency may indicate the use of opiates, after the salicylates and related analgesics do not prove sufficiently efficacious.

In neoplastic and other chronic, hopelessly incurable disease, pain is a major problem of management because of its progressive nature and prolonged duration. The management of pain in these patients requires considerable thought and planning because of the problem of tolerance.

In order to use addictive analgesics properly the practitioner needs to be equipped with a thorough knowledge not only of the analgesic actions but of all the other effects of these drugs. For this reason and because of the important role these drugs play in the relief of pain, they will be discussed in considerable detail.

Pharmacologic Aspects of Opiates

The opiates and other addictive analgesics have effects on every organ of the body, but only those pharmacologic actions which are pertinent to the present discussion will be presented here. Since morphine is the classic drug for the relief of severe pain and is the standard agent with which all other analgesics are compared, its pharmacologic action will be discussed in detail. Subsequently these facts will be used to compare the effects of the other addictive drugs.

Morphine.—

CENTRAL NERVOUS SYSTEM.—Morphine and other opiates exert their most important action on the central nervous system, particularly on the cerebrum and medulla. The cerebral effects are characterized by a change in mood and attitude and by disturbance in mentation. These are seen with the usual therapeutic doses (8 to 10 mg.). Within a few minutes after morphine is administered, the individual experiences a generalized muscular relaxation followed by a change of mood and attitude characterized by euphoria or a feeling of well being. Any preoccupation, worries, fears, inhibitions, and doubts which exist in the individual's mind decrease and soon disappear, and he becomes free of anxiety, content and loquacious.

ANALGESIC ACTION.—The relief of pain by morphine is the outstanding effect of the drug and, from a clinical standpoint, its most important action and one which is exerted wholly within the central nervous system. It is the general consensus that opiates relieve pain by (1) decreasing or inhibiting the perception of pain, (2) altering the psychologic reaction associated with such perception, and (3) inducing lethargy or sleep.

Effect on Mood. I have no doubt and there is general agreement that the most important effect of these drugs is on the reaction phase of the pain experience. *The aforementioned cerebral effects, especially the change in mood and attitude,* usually alter the psychic reaction to pain so markedly that the individual is no longer disturbed by it. The pain is perceived, but it no longer brings forth the usual responses such as anxiety, fear, panic, withdrawal, and flight. Consequently the patient is capable of tolerating pain because it is freed of its implications. These effects are similar to those of surgical prefrontal lobotomy and have in fact been referred to as a form of pharmacologic lobotomy. The obvious conclusion is that the change in the spectrum of the psychic reaction to pain is not only an important part of the analgesic action of morphine and other narcotics, but the primary and essential part of it.

with consequent marked hypotension, anoxic hypoxia, hypercarbia, tachycardia decrease in myocardial efficiency, and inverted T waves Movement of the morphinized patient from the supine to the sitting or semierect position may be followed by vascular collapse This is especially likely to occur in elderly patients and is probably on the basis of the generalized vasodilatation, which can be compensated while the patient is supine but cannot be overcome in the erect position

BRONCHIAL TREE —The bronchial musculature is stimulated resulting in a slight contraction but this effect is rarely if ever apparent from the use of therapeutic doses in normal man In the asthmatic patient, however, it may precipitate an attack

ABSORPTION, FATE, AND EXCRETION —Morphine and the other opium alkaloids are readily absorbed from the gastrointestinal tract and subcutaneous and intramuscular tissues, but not through the intact skin Following administration by these routes, there is a significant variation in the rate of absorption resulting in a difference in the time when the effects of the drugs manifest themselves This is particularly true following subcutaneous injection because of the variability of the cutaneous and subcutaneous circulation Under normal conditions following subcutaneous injection of morphine, about 60 per cent is absorbed from the site of injection during the first 30 minutes

Ninety per cent of the morphine is destroyed in the body tissues, particularly in the liver, and the rest is excreted unaltered by way of the urine and the feces Following absorption, most of the drug in some altered form is stored in the liver and skeletal muscles Detoxification proceeds slowly, and although the narcotic effects following a single dose are usually over in 4 to 6 hours, only 50 per cent of the amount is detoxified in the first 24 hours, and it is not until about 36 hours after injection that 90 per cent is destroyed About 10 per cent of the morphine is excreted in the urine and in the feces The end products resulting from its detoxification are eliminated by the kidneys

DOSAGE —The optimal analgesic dose of morphine will vary considerably depending on the age, weight, and physical status of the patient, the intensity of his pain the reflex irritability of his nervous system and the presence of existing diseases which increases reflex irritability However, excepting extremes in ages, the intensity of pain is the most important factor in determining the amount of morphine required for adequate relief Since this subject will be discussed in detail in a subsequent section, nothing more will be said here except to emphasize that *routinization of the indication and dose of morphine or any other analgesic* is haphazard therapeutics and is to be deplored

Experimental and clinical studies have shown that the optimal dose of morphine in the average 70 Kg (150 pound) adult varies from 8 to 15 mg In laboratory investigations it has been noted that in the adult the threshold for pain perception was increased by morphine as follows 32 per cent with 5 mg, 47 per cent with 8 mg, 60 per cent with 10 mg, and 71 per cent with 15 mg Beyond the 15 mg dose, increments produced increasingly smaller increments in the intensity of analgesia The maximum analgesic effect was reached in 90 minutes and duration of analgesia was 4 to 7 hours Since these studies were carried out with experimental pain they do not indicate the effect of morphine on the re

reflex, probably through central effects The well known phenomenon of pupillary constriction of morphine is also a central effect Therapeutic doses of this drug have little or no effect on the electroencephalogram but may cause an increase in intracranial pressure Morphine usually enhances two neuronal (stretch) reflexes, but depresses multineuronal (nociceptor) reflexes

GASTROINTESTINAL TRACT —Morphine, like all other phenanthrene derivatives of opium, tends to cause contraction of all smooth muscles, with the notable exception of those of the blood vessels This is in contrast to the benzylisoquinoline derivatives (papaverine) which cause relaxation of smooth muscle Morphine, therefore, causes an increase in tone of the gastrointestinal tract, particularly its sphincters This results in decreased motility and a consequent increase (up to 12 hours) in the emptying time of the stomach and a decrease in secretions of the gastrointestinal tract The resulting delay in the passage of the contents allows water to be more completely absorbed, which further delays its advance This, coupled with the increase in tone of the anal sphincter and the decrease in the (central) perception of the normal sensory stimuli of the defecation reflex, causes constipation, which may be severe after large doses of opiates In passing it should be pointed out that the delay in gastric emptying time following the administration of morphine will greatly delay the absorption of other drugs subsequently administered

BILIARY TRACT —Morphine causes a similar increase in the tone of the smooth muscle of the biliary tract which with large doses progresses to spasm, particularly of the lower end of the common bile duct Consequently there is increase of the intrabiliary pressure up to as much as 10 to 15 times the normal value It is obvious, therefore, that the pain relief afforded by morphine in biliary colic is a central effect Sometimes the administration of morphine aggravates the biliary muscle spasm so greatly that it may not be relieved by large doses of either atropine or papaverine, but requires the administration of an antispasmodic The function of the liver, as determined by the dye test is decreased for 6 hours following administration of morphine

GENITOURINARY TRACT —Morphine increases the tone, rate, and amplitude of contraction of the intact human ureter and detrusor muscles of the urinary bladder, whereas papaverine decreases them Although when given alone atropine has little effect on the ureter, it can eliminate the morphine-induced ureteral spasm It should be emphasized, however, that notwithstanding this pharmacologic action, morphine very frequently proves efficacious in relieving ureteral colic Obviously this relief is the result of its central action Morphine has antidiuretic effects In summary, then, the effects of morphine on the urinary tract are decreased urinary output, increased urinary urgency, and increased difficulty in micturition The normal contraction of the uterus during labor is not significantly affected by analgesic doses of morphine, but the intervals between contractions may be increased

CARDIOVASCULAR EFFECTS —Morphine and its congeners produce negligible effects on the heart and blood vessels, except for mild peripheral vasodilatation, which in the supine position has little effect Changes which may occur following their administration are due to lessened muscular activity, sleep, decreased metabolism, and respiratory depression Rapid intravenous administration of full therapeutic doses (10 mg) may result in severe respiratory and myocardial depression

codeine which in the past have been underrated Moreover, it is apparent that codeine in optimal doses is definitely inferior to morphine

Clinically it is a well appreciated fact that 10 mg of morphine is more efficient in relieving severe pain than 64 mg of codeine The difference is probably due to the lesser effects of codeine than morphine on the perception and the reaction phase of pain The psychologic effects such as modification of mood elimination of preoccupation and worries, and production of feeling of well being (factors which are the primary targets of the analgesic action of narcotics) are not as prominent with codeine as they are with morphine

DOSAGE —The dose of codeine for controlling mild to severe pain varies from 15 to 64 mg Since doses greater than 64 mg merely prolong analgesia but fail to produce a commensurate increase in degree of relief, there is no advantage in using larger amounts, except in the presence of tolerance Therefore it is better to give optimal doses at more frequent intervals

ROUTE OF ADMINISTRATION —It should be emphasized that the maximum effect of codeine is obtained by parenteral administration Therefore, it is wise to use it orally only for mild pain In order to achieve maximum analgesic effects in the presence of severe pain it should be administered subcutaneously in doses 30 to 64 mg, depending on the size age, and physical status of the patient and the intensity of his pain In controlling severe pain in circumstances in which morphine is not available, codeine in 64 mg doses may be injected intravenously, but slowly

Dihydrocodeine (Paracodin) —Dihydrocodeine is an analogue of codeine which has been used extensively in Europe and Central and South America for the past 45 years but apparently has escaped the attention of the American physicians In recent years Beecher and his associates have studied this drug in postoperative patients with sustained wound pain and they noted that 30 mg of dihydrocodeine produced analgesia which was almost equal both in degree and duration to that produced by 10 mg of morphine Concerning side effects they found that dihydrocodeine produced considerably less depression on respiration and less nausea and euphoria Indeed in their studies it was shown that 30 mg of dihydrocodeine produced no more side effects than a placebo This is in contrast to equianalgesic (60 mg) doses of the parent compound codeine which produced significant side effects Keats and his associates found 60 mg of dihydrocodeine to be the analgesic equivalent of 10 mg of morphine However with this dose respiration was depressed almost as much as following 10 mg of morphine It was also found that 90 mg of dihydrocodeine produced no greater analgesia than did 60 mg Moreover, the analgesia with this large dose did not exceed the analgesia of 10 mg of morphine Ruch and Ruch studied this drug in obstetrical patients and found 30 mg of dihydrocodeine to be the analgesic equivalent of 75 mg of meperedine They noted that dihydrocodeine produced significantly less respiratory depression of the infant and of the mother than did other analgesics

DOSAGE —It appears that dihydrocodeine is an effective analgesic for moderate pain The dosage range of dihydrocodeine in adults is 30 to 60 mg The drug is effective orally and parenterally although the subcutaneous intramuscular routes produce more prompt and more effective analgesia

action phase of pain consequent to disease, which as previously mentioned is the primary target of morphine and other addictive analgesics

Clinical investigation in patients with pathologic pain have shown that 8 to 10 mg of morphine administered subcutaneously will afford relief from moderate postoperative pain to over 90 per cent of patients In the presence of severe pain 10 mg of morphine provided relief to 65 to 70 per cent of patients, and 15 mg to approximately 80 per cent for periods of 6 to 8 hours Administration of 10 mg of morphine by the oral route produced relief in 40 per cent of the patients as compared to 30 per cent with placebo This demonstrates the ineffectiveness of morphine when administered by mouth probably due to slow absorption

The best approach to the problem is to try what is considered the optimal dose and if this proves ineffective to give a larger amount after the proper interval of time A crude yardstick for subcutaneous doses is as follows 0 8 mg per 15 pounds body weight for mild to moderate pain 1 mg per 15 pounds body weight for very severe pain If the pain is extremely severe it is advisable to administer the drug intramuscularly or better still to administer 0 8 mg per 15 pounds body weight intravenously over a period of 3 to 5 minutes Because of its ineffectiveness when given orally morphine should always be given parenterally

Codeine—Codeine is second only to morphine as a drug of choice to relieve pain It is frequently employed to relieve mild to moderate pain that cannot be controlled with a nonaddictive analgesic but is not sufficiently intense to warrant the use of a potent narcotic As previously mentioned codeine is often combined with nonaddictive analgesics and hypnotics

Pharmacology—Pharmacologically codeine resembles morphine except that its effects are milder In optimal doses it produces less sedation respiratory depression and gastrointestinal urinary and pupillary effects than morphine Nausea emesis constipation and diarrhea are seen less frequently and tolerance develops slower than with morphine Although codeine is an addicting drug its addiction potential is less than any of the other opiates It is these advantages of codeine which indicate its use before more potent and more addictive drugs are employed in managing patients with chronic pain

Comparison of Codeine With Morphine—Even when employed in the maximum dose codeine is not as effective in relieving severe pain as 10 mg of morphine Thus it was found that 64 mg of codeine increased the threshold of experimentally induced pain approximately 50 per cent above normal as compared to 60 per cent with 10 mg of morphine Moreover the duration of this action was shorter with codeine In controlled clinical studies made in postoperative patients with steady pain it has been found that 60 mg of codeine administered by mouth produced relief in 40 per cent of trials as compared to 33 per cent relief with placebo However when the same amount of the drug was given subcutaneously it provided relief to 60 per cent of the patients as compared to 71 per cent with 10 mg of morphine It was found that increasing the dose from 30 mg to 120 mg resulted in a real increase in analgesic potency although beyond 60 mg the principal advantage was in duration of effect However, it was noted that troublesome side effects with doses of 60 to 120 mg of codeine were as frequent as with 10 mg of morphine These results emphasize the potency and toxicity of

The usual clinical dose is 3 mg in an average adult Since the drug is m keted only in 3 mg oral capsules, it is difficult to administer smaller doses H ever, because this drug is usually reserved for patients with severe intractable p due to neoplastic disease, this preparation is appropriate With development tolerance it will be necessary to give 6 mg or a larger amount to control sev pain *Despite the early optimism concerning its place as a specific narcotic* cancer patients metopon has been found to offer no significant advantages o *the standard drug*

Heroin —*Heroin diacetylmorphine, is usually prepared as the hydrochlor salt It is one of the most potent analgesics of the morphine derivatives In eq* doses it is 5 to 8 times as potent, but also 5 to 8 times as depressant as morphi It is therefore employed in one fifth to one eighth the dose of morphine. W doses of 1 to 2 mg administered subcutaneously, it brings about relief of pain mc quickly than the other opiates but its duration of action is much shorter than th of morphine Heroin causes a most intense euphoria, which often supplar marked subjective depression Moreover, unpleasant side effects such as nause vomiting and constipation, seen with other opiates are not as common wi heroin As will be seen subsequently, these properties of heroin—its ability the most potent euphoric agent and the absence of side effects—are responsib for the serious nature of addiction to this drug For these reasons, its importatio *manufacture and sale in the United States are prohibited by law*

Pharmacology of the Opioids

Meperidine (Demerol) —Demerol synthesized in Germany in 1939, was th first practical synthetic, morphinelike analgesic and as such was the first of th opioids The promise of an effective substitute for morphine caused Demer immediately to gain widespread popularity and to be submitted to extensive clin cal investigation Introduced under the trade name of Demerol in America th drug is also known as isonipecaine, in Britain as pethidine and has the offic name of meperidine

COMPARISON OF MEPERIDINE AND MORPHINE —

Relative Effectiveness Early investigations seemed to indicate that Demer had an analgesic potency greater than that of codeine and slightly less than tha of morphine *In one investigation it was found that 75 to 100 mg* of Demer given parenterally every 3 to 4 hours was capable of completely controlling post *operative pain in 91 5 per cent* of the patients and afforded moderate relief in a additional 5 2 per cent In another well controlled study it was noted that 50 mg of Demerol produced relief in the same per cent of trials as did 10 mg of mor phine whereas 100 mg provided relief a significantly greater number of times

Effects on Central Nervous System Demerol produces cerebral effects simi lar to morphine but of a lesser degree When a full therapeutic dose is adminis tered to a patient with pain or anxiety, the ensuing analgesia may result in euphoria and finally sleep However, in patients without pain *these effects are less indeed dysphoria may result* Though it is generally accepted that Demerol causes less *respiratory depression than morphine* available quantitative data clinical observa t ons and reported cases of serious depression following its use negate claims of

Pantopon —Pantopon, also known as omnopon and pantopium, is a mixture the purified opium alkaloids in the same proportions which occur naturally hus it is a purified opium devoid of inert material which contains close to 50 r cent morphine by weight As might be expected, its analgesic potency is not eater than that produced by optimal doses of morphine despite other claims ade for this drug In experimentally induced pain 20 mg of Pantopon produced e same effects as 8 mg of morphine Moreover, claims made for Pantopon that produces fewer side effects than morphine and provides in addition to the anal sic action of morphine the antispasmodic action of papaverine are not sub-antiated clinically This is as might be expected because its papaverine con-nt is too small Pantopon is available for oral use and for parenteral injection

Dihydromorphinone —Dihydromorphinone, commonly known as Dilaudid, e first biosynthetic derivative of morphine is one of the most potent of the opiates a weight basis Clinically 2 mg of this drug produces analgesia which is ghtly more intense than that following administration of 10 mg of morphine owever, its analgesic action is definitely briefer, it does not cause quite as much phoria, and is markedly less sedative The latter quality may be employed to lvantage in patients in whom it is desired to provide relief of pain without caus-g sleep

The other pharmacologic effects of Dilaudid are similar to those of morphine cept that such side effects as nausea vomiting and constipation are less severe id frequent In equianalgesic doses, respiratory depression is slightly less with ilaudid than with morphine Dilaudid is effective by the oral and rectal routes nce tolerance and addiction occur with Dilaudid, it has no advantage over mor-ine in this respect Indeed, the greater frequency with which dihydromorphinone ust be given for chronic pain increases the possibility of addiction and tolerance

[Hydroxydihydromorphinone (oxymorphone, Numorphan) is the latest mor-ine congener to be added to the list Too little is yet known, and there has been o little general experience with it to justify a conclusion that it has any real lvantages over morphine Ed]

Metopon —Metopon, another synthetic opiate derivative, is the methyl ana-gue of Dilaudid and has some of the characteristics of the latter Metopon has any of the pharmacologic properties of morphine with the following differences 1) it is more rapid acting and more potent than morphine on a weight basis, 2) it is effective orally, (3) following subcutaneous injection, it produces more apid analgesia, (4) addiction and tolerance develop more slowly than with mor-hine and there is relatively rapid resolution of the abstinence syndrome following ithdrawal of the drug

The early claims that equianalgesic doses of metopon produce less frequent nd milder side effects has not been substantiated clinically Recent, well con-olled clinical studies have shown that respiratory depression, nausea, vomiting, rowsiness, sleep, and other undesirable actions occurred as frequently (and occa onally more frequently) with 3 mg of metopon as with 10 mg of morphine n experimentally induced pain 6 mg raised the pain perception threshold nearly 00 per cent Clinical studies have shown that 6 mg produced relief in 100 per ent of the doses, while 3 mg was as effective as 10 mg of morphine

the analgesic action of Demerol lasts approximately 3 to 4 hours, which is somewhat shorter than that of morphine

Alphaprodine —Alphaprodine (Nisentil) is a close congener of Demerol It is a rapid, short acting, potent analgesic with significant sedative effects

In subjects with experimentally induced pain, the pain perception threshold is said to be increased 100 per cent with maximal therapeutic doses Administration of 60 mg subcutaneously during the first stage of labor when pain is severe results in complete relief in 80 to 92 per cent of the trials Clinical studies of postoperative patients have shown that 40 mg of Nisentil is the equivalent analgesic dose of 10 mg morphine Following subcutaneous administration maximal effect occurs in 8 to 15 minutes and lasts 1½ to 2 hours Intravenous injection produces maximum analgesia within 5 minutes and relief lasts less than 1 hour

UNTOWARD EFFECTS —Untoward effects are similar to those described for morphine and Demerol Nisentil produces greater respiratory depression than equianalgesic doses of Demerol It is an addictive drug

DOSAGE —The dose for the relief of moderate pain is 0 25 mg per pound of body weight and of severe pain about 0 4 mg per pound of body weight These doses which are approximately 40 mg and 60 mg, respectively, for an average adult, may be repeated every two hours if necessary The drug is effective orally and parenterally Because of its rapid action the subcutaneous route is adequate for most patients who require parenteral injection Intravenous injections increase the hazard of respiratory depression and should be performed slowly and only in urgent situations

Anileridine (Leritine) —Anileridine is another relatively new analgesic drug which is an analogue of meperidine (Demerol) During the past several years it has been investigated extensively as an analgesic agent in the management of various types of pain including postoperative pain, labor pain and also as a supplement to general anesthesia

PHARMACOLOGIC PROPERTIES —The analgesic potency of anileridine has been studied by various investigators including Keats and his associates who found 40 mg of anileridine to be the analgesic equivalent of 100 mg of meperidine, while 50 mg of anileridine exceeded 100 mg of meperidine in analgesic potency Similar results have been reported by Dripps and his associates who found that 25 mg of anileridine injected intramuscularly produced the same degree of pain relief as did 10 mg morphine From their results it was indicated that following intramuscular injection the equianalgesic dosage ratios appeared to be morphine 1 and anileridine 2 to 2 5 and with meperidine 3 5 to 5 The duration of relief was approximately the same with anileridine and meperidine but considerably longer with morphine

These and other clinical studies indicate that anileridine is a potent analgesic agent which is adequate for the relief of moderate to severe pain

UNTOWARD EFFECTS —The aforementioned well designed clinical studies revealed that anileridine in doses of 40 mg depressed respiration as much as 100 mg of meperidine but this depression was of significantly shorter duration than that following Demerol Thus Keats and co workers found that while 40 mg of anileridine depressed respiration as much as did 100 mg of meperidine after 3

the original investigators that Demerol is devoid of such hazard Respiratory depression of the newborn infant is occasionally seen following analgesic doses of Demerol given to the mother less than 45 to 90 minutes prior to delivery Moreover, in infants and young children, in the aged, and in patients with expanding intracranial lesions, it may cause significant respiratory depression

Other central nervous system effects of Demerol include no significant alteration of the pupil, no depression of the cough reflex, and less hypnotic effect than morphine It causes less nausea and vomiting than morphine However, overdose of Demerol is frequently accompanied by excitement, uncoordinated jerky movements, and other manifestations of central nervous system stimulation

Gastrointestinal Effects In contrast to morphine, Demerol relaxes smooth muscle except that in the duodenum, the biliary tract (especially the sphincter of Oddi), and the jejunum The intensity of the spasmogenic effect in the upper gastrointestinal tract is greater than that produced with codeine, but considerably less than that of morphine Constipation and alteration of bowel habits are less frequent with Demerol than with morphine It should be noted that typical attacks of biliary colic may be precipitated with Demerol, but these can be regularly (although briefly) relieved by the inhalation of amyl nitrite Demerol, like morphine, produces relief of biliary colic by its central effects The spasmolytic effects on the bronchial tree and ureters are less than originally thought The drug does not significantly alter the activity of the normally contracting uterus but appears to increase the tone, frequency and intensity of contractions in the uterus made hyperactive by oxytocics

Other Effects Like morphine, Demerol causes vasodilatation and, if the patient assumes the upright position, hypotension, tachycardia vertigo, and even syncope The frequency of vertigo limits the use of this drug in the ambulant patient Other untoward side effects include profuse sweating, dryness of the mouth, and flushing of the face

Addiction Danger Habituation and addiction to Demerol are a serious menace, although they develop more slowly than with morphine Therefore the same cautions and restrictions should be observed as with morphine

Dosage —The dose of Demerol is approximately 10 times that of morphine An approximate dose scale is 0 75 mg per pound of body weight, not to exceed 150 mg Very frequently 50 mg is sufficient to relieve mild to moderate pain particularly in older patients, and most adults can be afforded relief with 100 mg The maximum dose of 150 mg should be reserved for vigorous patients with severe pain If this dose is ineffective, a smaller dose (50 mg) is given intravenously or another drug is tried

Demerol can be administered orally, but the results are less satisfactory than following intramuscular injection Although it is considered irritating to the skin, the subcutaneous route can be employed to advantage when only a few doses are to be given In urgent situations the drug may be administered intravenously, but must be injected slowly, or *severe* untoward reactions particularly dizziness, restlessness, flushing, tremors, and even convulsions and syncope may occur In a few instances the writer has seen cardiovascular collapse following a rapid dose of 50 mg in elderly patients Following subcutaneous and intramuscular injection,

orphine to patients who have received large doses of narcotics for analgesia during the first stage of labor reduces markedly neonatal respiratory depression The uterine tone progress of labor, and postpartum course are unaffected by nal orphine Severe respiratory depression or apnea of newborn infants consequent to narcotic analgesia of the mother is effectively overcome by nalorphine This antagonist also prevents or relieves morphine induced biliary spasm and elevation of cerebrospinal fluid pressure

It should be emphasized that nalorphine *is not effective in preventing or abolishing respiratory depression and other depressant effects of barbiturates gen eral anesthetics nonnarcotic agents,* or *pathologic states* Indeed, it may even ag gravate the *depression in such instances*

In subjects actively addicted to morphine or other narcotic drugs nalorphine produces effects indistinguishable from the acute morphine abstinence syndrome The symptoms reach their peak in 30 to 45 minutes, and last 2 to 3 hours These properties make this drug very useful in the diagnosis of addiction Obviously it cannot be used in the treatment of addiction Nalorphine has been known to induce the abstinence syndrome in persons who have received as little as 15 mg of morphine 4 to 5 times daily for only a few days

Mode of Action The mechanism of action is not definitely known but it is thought that it acts as a competitor with the narcotics According to this theory the narcotics have an affinity for receptor and effector cells in the neuraxis The narcotic antagonist displaces the narcotic analgesic from the receptors

CLINICAL USE AND DOSAGE —Nalorphine has proved most useful in the treat ment of acute narcotic intoxication In such cases intravenous administration of *5 to 10 mg often produces dramatic effects the respiration and circulation* return toward normal within 3 to 4 minutes If the increase in pulmonary ven tilation and other beneficial effects are not sufficient in 10 to 15 minutes the dose *is repeated* Total dose should not exceed *40 mg This provides a good margin* of safety since doses of 10 to 15 mg are usually effective in the average case In newborn infants the dose is 0 2 to 0 4 mg diluted in 2 to 3 ml of normal saline injected into the umbilical vein In older children the dose is *0 1 mg* per *kilogram* of body weight

Recently premixed solutions of nalorphine and one of the narcotic analgesics have been combined in various ratios to effect analgesia without respiratory de pression The published results have not all been favorable In one study a com bination containing nalorphine and *morphine in the ratio of 1 2 produced analgesia* and side effects similar to those produced by morphine alone *Under* other cir cumstances the mixture resulted in more profound respiratory depression and sedation than morphine alone Obviously until critical ratios have been definitely established such combinations cannot be recommended for general use

Levallorphan (Lorfan).—Levallorphan more recently synthesized than nal orphine has the same structural relationship to levorphan (Levo Dromoran) as nalorphine has to morphine

COMPARISON OF LEVALLORPHAN AND NALORPHINE —The pharmacology of lev allorphan resembles that of nalorphine On a weight basis it is approximately 4 to 5 times as potent as nalorphine

hours respiration had returned to control levels following anileridine, whereas respiration remained depressed following meperidine Dripps and co workers found itching, nausea, vomiting, and euphoria following the administration of anileridine as with other narcotics

Studies on human volunteers and animals indicate that anileridine, unlike meperidine, does not cause liberation of histamine, a fact of significant clinical importance Development of tolerance to anileridine is said to be less and more *gradual than to morphine Although the addiction potentiality of anileridine has* not been determined in detail, it has been shown that the drug is addictive

Dosage —Anileridine is available in 25 mg tablets for oral administration and as sterile solutions containing 25 mg per milliliter for parenteral use The recommended oral dose in adults is 25 mg, repeated every 4 to 6 hours if necessary, in treating mild to moderate pain and 35 to 75 mg for severe pain However, in cases of severe pain it is preferable to inject the drug subcutaneously or intramuscularly in doses of 25 to 50 mg As in the case of morphine, intravenous administration of the drug may be employed for a more prompt and more marked effect However, it should be stressed that small doses should be employed and the injection be carried out very slowly lest the patient develop marked respiratory depression, which may progress to apnea and/or marked hypotension

[Ethoheptazine (Zactane) is a feebler and apparently nonaddictive congener of meperidine It is available in a mixture with aspirin Ed]

Methadone (Dolophine) —Methadone is a comparatively new synthetic compound with pronounced analgesic properties produced by German chemists during World War II Methadone is a heptanone derivative which is also known as Dolophine, Adanon, and amidone

Comparison of Methadone and Morphine —Methadone exerts many pharmacologic actions which are strikingly similar to morphine, particularly analgesia

Effectiveness It is a slightly more potent analgesic than morphine In experimentally induced pain 10 mg of methadone raised the pain perception threshold 100 per cent Several clinical investigators report moderate to complete relief of pain in over 85 to 90 per cent of patients As a rule, pain is relieved without significant sedation Like morphine, the focus of the analgesic action of methadone is in the central nervous system

Addictive Characteristics Methadone produces only mild euphoria in non addicted patients when used for the relief of pain On the other hand, in addicts and postaddicts a large dose of this drug produces euphoria which is as intense as that produced by morphine and other potent opiates and persists longer Moreover, in these patients methadone prevents or completely alleviates the morphine abstinence syndrome Therefore it can be employed in the therapy of opiate addiction Tolerance to methadone develops more slowly than to morphine Upon abrupt withdrawal of methadone the abstinence syndrome develops more slowly, is less intense and more prolonged than the abstinence syndrome of morphine

Other Effects Maximal analgesic doses of methadone depress respiration and the cough reflex, increase intestinal tone and the amplitude of contractions, and produce smooth muscle spasm and miosis, almost but not quite to the same degree

following its intravenous administration have been reported Urticaria, skin rash and contact dermatitis may occur

Abnormal responses to the analgesic effects have also been reported *in sor* sensitive individuals Codeine *may cause severe epigastric pain*, and hyperalges may occur in hypersensitive individuals following the disappearance of the an- gesic effects

Infants and aged and debilitated patients are more susceptible to depressa effects of narcotics, and the dose should therefore be reduced Care must be take *in administering morphine* for a prolonged period of time to pregnant women fo the drug passes the placental barrier and enters the tissues of the fetus Indee the newborn infant may show withdrawal symptoms if it has been repeatedly e posed to morphine in utero

In adults, existing pathologic states which may or may not be causing the pa *for which* analgesics are being given may cause abnormal responses to the narcotic The administration of small therapeutic doses of a narcotic to patients with myx edema may be followed by a severe depression, whereas hyperthyroidism increase the tolerance to the drugs Patients with increased intracranial pressure may show marked depression following the administration of usual doses of morphine or an other narcotic analgesic, whereas patients with psychoses or fever may becom excited The use of morphine in patients with hypertrophied prostate or uretera stricture may precipitate acute urinary retention Deaths have been reported fol lowing the administration of morphine to patients with bronchial asthma

A change in position from the horizontal to the vertical after administration o morphine may be followed by cardiovascular collapse This complication is prob*ably due to a generalized vasodilatation and consequent depression of homeostati reflex mechanisms and uncompensated drop in blood pressure* It *is* particularly important when morphine is administered to ambulatory patients who have serious cardiovascular disease

OVERDOSAGE —Acute narcotic poisoning occurs following inadvertent clinical overdosage or as a result of a suicidal attempt The amount of morphine necessary to cause acute poisoning varies *with the individual's tolerance The susceptibility* of infants of the aged, and of adults with certain diseases has been mentioned A normal adult with severe pain (which is an antagonist to opiates) can tolerate up to a 60 mg dose, whereas, if pain is not present, such a dose will prove toxic Of course, the addict can tolerate 20 to 200 times the therapeutic dose In normal adults a dose of *120* mg *of morphine is usually followed by serious symptoms* with larger doses the prognosis becomes progressively less hopeful, and with 240 mg death occurs as a result of the marked respiratory depression and consequent anoxia

Occasionally a delayed type of narcotic poisoning occurs in patients with im paired cutaneous circulation *resulting from shock, neurogenic* hypotension, or ex posure to cold Subcutaneous and even intramuscular injections of morphine in such circumstances may not be absorbed and thus may fail to give adequate relief of pain The unwary physician may repeat the administration of the drug one or more times in an effort to relieve the pain, but because of the impaired absorption the drug is ineffective until, *as a result* of therapy for the shock, the improvement

PHARMACOLOGIC EFFECTS.—When given in the absence of narcotics levallorphan produces slight analgesia and respiratory depression and other narcotic effects. However, when given after, together with, or before narcotics, it corrects or prevents respiratory depression and other undesirable effects.

Several clinical investigations in which levallorphan was combined with various narcotics to produce analgesia with minimal respiratory depression should be mentioned. Preliminary studies in postoperative or chronic pain indicate that a ratio of 10 parts levorphan to 1 part levallorphan provides good analgesia and adequate respiration. Administration of 0.03 mg. per kilogram of levallorphan combined with either 0.66 mg. per kilogram of alphaprodine (Nisentil) or 2 mg. per kilogram of meperidine (Demerol) effectively prevents respiratory depression and still produces analgesia.

CLINICAL USES AND DOSAGE.—The indications for levallorphan are the same as those for nalorphine. The initial adult dose is 0.5 to 1.0 mg. administered intravenously. Several small increments are preferred to large single doses. In infants and children the dose can be calculated on the basis of 0.02 mg. per kilogram of body weight.

Complications of Narcotic Therapy

It is apparent from the preceding discussion on the pharmacology of narcotic analgesics that inherent in their use are certain undesirable side effects which evidently cannot be divorced from analgesia. With proper use of these drugs these somewhat expected effects are of a minimal degree and, therefore, are of little concern. Occasionally, however, the undesirable effects are of such serious and malefic nature as to endanger the patient's life. These complications may occur as a result of overdose or prolonged administration. Overdose may be absolute or relative and is followed by acute toxic effects, whereas prolonged use of narcotics results in addiction.

Acute Toxicity.—

ETIOLOGY.—Acute toxic reactions may result from (1) attempt at self-extinction, (2) gross error in dosage, (3) abnormal response to usual therapeutic dose, (4) delay in absorption of repeated doses, or (5) sudden disappearance of severe pain soon after the administration of large therapeutic doses.

UNTOWARD REACTIONS TO THERAPEUTIC DOSES.—Sensitive reactions and other abnormal responses occasionally occur following administration of optimal therapeutic doses to patients who apparently have sensitivity or idiosyncrasy to narcotics. These abnormal responses are manifested by extremely severe and persistent nausea, vomiting, constipation, and central nervous system depression requiring active therapy. Some individuals, especially women, are excited by morphine and some of the other opiates, particularly codeine and heroin. In some unusual cases there is stimulation of the cerebrum resulting in tremors, rarely delirium, more rarely convulsions, and sometimes insomnia as a late sequel. Marked excitement is not infrequently observed after excessive doses of codeine. Heroin may cause central excitation and is taken by the heroin addict for its euphoric stimulation.

Allergic phenomena rarely, if ever, follow administration of narcotics. Wheals following subcutaneous injection of codeine and marked anaphylactoid reaction

methoxamine (*Vasoxyl*), 3 to 5 mg intravenously and 10 mg intramuscularly, or phenylephrine (*Neo Synephrine*), 1 mg intravenously and 5 mg intramuscularly, is preferable because these drugs do not accelerate the heart Of course, if there is shock, plasma or plasma expanders are administered

Other Measures Additional measures consist of maintenance of proper fluid and electrolyte balance, maintenance of normal temperature, frequent change in the patient's posture to obviate pulmonary complications, repeated catheterization to avoid distention of the bladder, and symptomatic therapy of itching, nausea, vomiting, and confusion during the recovery period Usually the narcotic antagonist decreases the severe gastrointestinal symptoms, but, if these persist, they may be relieved by administering an antiemetic drug such as Marezine, Dramamine, or Thorazine Usually doses of 50 mg intramuscularly repeated every 3 to 4 hours are effective

Narcotic Addiction —Prolonged consumption of morphine and other narcotic analgesics is inherent in the most serious complications of this method—addiction Addiction may be defined as the habitual and compulsive misuse of a drug in a manner productive of results which are harmful to the user, to society, or to both This condition is characterized by three principal phenomena tolerance, habituation, and physiologic-dependence Wikler adds a fourth to these the tendency to relapse to the use of the drug after repeated "cures" Although a detailed discussion of this problem is outside the scope of this chapter, the problem is of such importance as to warrant the following summary, which will serve as a basis for the discussion concerning the design for clinical use of addictive analgesics

TOLERANCE —Tolerance may be defined as the progressive diminution in the intensity of the effects to the same dose of drug in question during prolonged repeated use In patients medically addicted to narcotics given for control of chronic pain, the development of tolerance is usually first manifested by a gradual increase *in the amount of drug needed to provide the same degree of relief* Initially the patient may obtain sufficient analgesia with 10 mg of morphine, but, with repeated use of the drug at regular intervals, a progressively larger dose is required to control the pain This phenomenon may progress to such a point that the individual tolerates 20 to 200 times the ordinary therapeutic dose of the narcotic

For some unknown reason, tolerance does not occur to all manifestations of [illegible] to some of [illegible] ue to [illegible] n the other hand tolerance is developed to the euphoric effects, respiratory depression, lethargy and stupefaction and these fail to appear after continued use of the drug unless the dose is increased There seems to be no apparent limit to the tolerance of the euphoric or psychic effects Although the addict develops tolerance to the analgesic action of morphine, *fortunately this tapers off when 30 to 45 mg are reached* Thus, the morphine addict with pain will experience relief of the pain with relatively small doses of the drug which will not produce psychic effects

The time necessary to develop such tolerance varies with each drug and from individual to individual However, 2 weeks of continued use of the drug is the average time necessary to develop some tolerance to the depressant effects The

in the circulation leads to the sudden absorption of the morphine from the various sites and results in morphine poisoning

Another not infrequent cause of narcotic depression is administration of large doses for severe pain of a type which may suddenly lessen in severity or even disappear spontaneously For example, the excruciating pain of renal or biliary colic or coronary occlusion may disappear coincidentally following the administration of morphine which has justifiably been given in maximum doses As a consequence acute morphine poisoning develops

Symptoms Acute narcotic poisoning is manifested by central nervous system depression In mild cases the patient is asleep or stuporous, but in severe cases this progresses to coma which may be profound The respiratory rate may be 2 to 4 per minute, and as a result of the asphyxia a mottled cyanosis soon appears The pupils are symmetrical and pinpoint but, if anoxia supervenes, they may dilate markedly The blood pressure is at first maintained and may be even increased above normal due to hypercarbia but it soon begins to fall gradually because of deleterious effects of anoxia on the capillaries, with a consequent increase in their permeability and loss of blood proteins This eventually will lead to irreversible shock if treatment is not instituted

The triad of coma pinpoint and symmetrical pupils, and marked respiratory depression strongly suggests a diagnosis of acute morphine poisoning

TREATMENT —Treatment consists of use of narcotic antagonists and supportive measures to the respiration and circulation

Ventilation The first and most important step is to provide adequate ventilation for the patient so that the tissues are properly respired This is best accomplished by introducing an endotracheal tube and connecting it with an appliance which contains a source of oxygen and means for absorption of carbon dioxide Inasmuch as the main drive to respiration in patients with severe narcotic depression is the hypoxic stimulation of the carotid chemoreceptors, high tensions of the inhaled oxygen will probably cause apnea Then it will be necessary to ventilate the patient manually or by means of a mechanical ventilator

Narcotic Antagonists As soon as this initial step is accomplished, the patient is given a narcotic antagonist The initial dose is 5 to 10 mg of nalorphine (Nalline) or 0 5 to 1 0 mg of levallorphan (Lorfan) given intravenously If the increase in pulmonary ventilation is not adequate in 10 to 15 minutes, the dose is repeated Since a relative overdose of the antagonist (i e, a dose larger than necessary to reverse the effects of the narcotic) will aggravate the depression, an attempt should be made to titrate by using small increments rather than to hazard overdosage This is particularly important if the dose of the narcotic is unknown. Amounts of 10 to 20 mg of nalorphine or equiactive amounts of levallorphan are usually sufficient to dramatically restore normal respiratory and circulatory function It is essential, however, that the patient is observed for at least 24 hours

Circulation In severe toxicity the cardiovascular system is usually depressed and requires supportive measures In the early phases when hypotension is due to vasodilatation, vasopressors should be given If the hypotension is accompanied by a slow pulse, ephedrine, 25 mg intravenously or 50 mg intramuscularly, will effect a sustained rise in pressure and increase in pulse If the pulse is rapid

losis and loses weight At the end of the fifth to the seventh day these signs and symptoms subside and the patient begins to eat, drink, and sleep and rapidly regains his composure and weight

THERAPY OF NARCOTIC ADDICTION —With the exception of patients with painful fatal illness, the occurrence of narcotic addiction caused by treatment for illness is evidence of therapeutic failure

Diagnosis Diagnosis of addiction in patients is simple if the physician keeps in mind the comments made in connection with tolerance The presence of constricted pupils and scars or needle marks in the skin should arouse suspicion An absolute diagnosis can be facilitated by administrations of small doses (2 5 mg) of nalorphine or (0 5 mg) levallorphan

Management The management of narcotic addiction is a highly specialized problem requiring a well integrated program that includes expert medical psychiatric and nursing care and cannot be discussed here

DESIGN FOR USE OF ADDICTIVE ANALGESICS FOR RELIEF OF PAIN

Principles —The primary purpose of the preceding detailed discussion concerning the effects and complications of narcotic analgesics was to emphasize the serious nature of their clinical use The exigencies of a busy clinical practice are often conducive to their improper use, which not infrequently results in complications In order to minimize this risk it is necessary for the physician to consider carefully many of the details previously discussed

At the risk of belaboring points already made, it should be stressed that the cause of pain must be ascertained and, if possible, eliminated rather than masked by drugs On the other hand, analgesics may be useful in giving relief while attention is directed toward determining and treating the fundamental etiologic basis of pain Moreover, the physician should not use addictive analgesics when other medicaments will accomplish the same end As previously stated, nonnarcotic analgesics alone or in combination with sedatives and hypnotics are frequently effective in relieving mild to moderate pain, especially that from integumental structures When these no longer prove adequate, they may be combined with codeine, dihydrocodeine, or with small doses of Demerol It should be stressed that the use of narcotics should be postponed until they are specifically needed This is not to say that narcotics should be avoided, but they should be reserved specifically for control of moderate to severe pain in patients in whom other drugs or methods have failed or are contraindicated

Assuming that addictive analgesics are indicated their proper prescription requires acceptance of certain premises The relief from pain with this or any other method is always obtained at a price exacted from the patient in the form of psychologic and physiologic deviations or depletions Although with proper application the price may be relatively small there is no addictive drug which is devoid of undesirable effects Indeed one of the most notable profits derived from recent clinical studies of addictive analgesics is the belated realization that in equivalent analgesic doses they all produce remarkably similar undesirable effects

It is the primary mission of the physician to select the drug of choice and use

larger the dose and the more frequent and regular the administrations, the quicker tolerance develops The importance of prescribing the smallest dose which will provide adequate relief from pain is obvious Cross tolerance exists between the various alkaloids, and a person tolerant to morphine is also tolerant to dihydromorphinone (Dilaudid), heroin metopon, and codeine When medication is discontinued, tolerance usually disappears within a few days to several weeks, depending on the duration and degree of tolerance After this interval small doses will again produce analgesia and depressant effects, but, if the continued use of the drug is resumed, tolerance develops more rapidly than it did initially

HABITUATION —Habituation refers to the psychologic and emotional dependence on the drug The drug provides a mental "crutch," without which the addict is anxious, unhappy, depressed, and irritable The situation arises primarily because the patient has realized that the drug provides relief from anxiety, tension and the need for psychologic adaptive behavior Psychologic dependence requires a certain readiness and there are several predisposing factors which make it one of the leading hazards in prescribing addictive drugs These include pre-existing alcoholism, psychoneurotic tendencies, extreme degrees of anxiety overdependence, and previous psychotic episodes

PHARMACOLOGIC ADDICTION —Pharmacologic dependence refers to a phenomenon which is closely related to tolerance and signifies the basic physiologic need for the narcotic the abrupt withdrawal of which is followed by an 'abstinence syndrome'

Abstinence Syndrome The abstinence syndrome is characterized by development of the psychosomatic and autonomic complex of signs and symptoms clearly manifesting physiologic dependence on the drug These signs and symptoms appear within 4 to 12 hours after the last dose of the opiate is omitted and they progress in degree so that within 48 hours they are severe, reach their peak in 72 or 96 hours and thereafter regress so that at the end of the fifth to the seventh day they usually cease

The first signs are yawning, lacrimation rhinorrhea, sneezing, perspiration anorexia and tremors—all of which are usually mild These are soon followed by restlessness, irritability mental depression, muscular weakness dilated pupils, and increased respiratory rate At this point the addict strongly indicates the desire for the drug All of these manifestations progress to an exaggerated degree The weakness and depression become pronounced as do the nausea vomiting and diarrhea He usually experiences bouts of chills alternating with flushing Severe muscle tremors, twitching, rigidity, headache, diplopia delirium and occasionally mania also develop Not infrequently severe myalgia of the abdomen, chest back, and extremities, simulating visceral disease, occurs

At the end of the first 8 hours or thereabouts, the addict falls into a deep sleep which may last from 8 to 12 hours, but from which he awakens more irritable, restless, and miserable than before The syndrome may appear several times before the regression and final subsidence of the signs and symptoms take place During the 4 or 5 days in which the signs and symptoms are very severe, the patient becomes dehydrated as a result of the vomiting diarrhea, and sweating coupled with the failure to take fluids and food As a consequence he develops acidosis or alka

prescribing the analgesic drug and assuming without follow up that the patient had relief of pain because this was the amount (and type) of medication advocated for this condition is to be deplored Moreover, care must be exercised in avoiding labeling the patient as psychoneurotic or hypersensitive because the prescribed dose is not adequate If proper evaluation indicates that the type and dose of the analgesic afforded adequate relief the same dose should be given if pain returns with the previous intensity Otherwise the dose is altered accordingly

Optimal Mode of Administration —

ORAL —The oral route is the most convenient to all concerned and the least uncomfortable to the patient It is therefore, indicated in managing chronic pain However it has the disadvantage of variation in the rate and degree of absorption consequently the degree of analgesia is not strictly predictable

SUBCUTANEOUS —The subcutaneous route is most commonly employed to administer narcotics for the relief of pain The action of the drug is more uniform and of longer duration than by any other route, the 'peak action is not as high as it is following intramuscular or intravenous administration and, therefore the unpleasant side effects are not as marked However, as previously stated this route should be avoided in patients with impaired cutaneous circulation that may result from shock, neurogenic hypotension or exposure to cold

INTRAMUSCULAR —The intramuscular route is employed when the oral or subcutaneous routes are contraindicated or when quicker action is desired It has the advantage over intravenous administration in that the action of the drug is more uniform of longer duration and the peak effect is slightly less and therefore the unpleasant side effects are of a lesser degree

INTRAVENOUS —On the other hand, intravenous injections of narcotic analgesics afford a means of giving effective pain relief almost immediately, although for a shorter period of time Following intravenous administration, morphine gives relief of pain within 3 to 5 minutes has a peak action in 10 to 30 minutes and lasts only 1 to 2 hours In addition any idiosyncrasy or abnormal sensitivity to the drug will be immediately manifested allowing the curtailment of the injection or if the total dose had already been given the physician knows of the abnormal effects immediately

The intravenous method should be reserved (1) for extreme emergencies such as severe coronary occlusion or injury accompanied by excruciating pain (2) for very severe almost intolerable pain associated with conditions which in themselves are not emergencies such as occurs with renal or biliary colic and (3) to obtain a short peak action for the management of severe pain of very short duration like that associated with painful manipulation or instrumentation Examples of the latter indication are the pain associated with the insertion of a cystoscope in a patient with urethral stricture, administration of the first enema to sensitive patients who have had a recent hemorrhoidectomy the changing of dressings in patients with severe burns and manipulation or reduction of a dislocation or fracture

The dosage of the various narcotics for intravenous injection is approximately two thirds to three fourths that for subcutaneous injection In order to avoid such unpleasant side effects as nausea, vomiting vertigo, tinnitus generalized

it in such a manner as to cause the least degree of disturbance of bodily function How effectively he discharges this grave responsibility depends primarily upon his knowledge, judgment, skill, experience, interest, and patience It is mandatory that he adhere strictly to the fundamental principles of good therapeutics, namely, (1) to give a specific drug for a specific indication, (2) to administer the drug in optimal doses, i e, the smallest amount which will cause the desired effects, (3) to administer it by the optimal route These entail individualization of type and amount of drug and the route of administration for the particular patient and the particular pain From almost every standpoint the management of chronic, intractable pain must be considered quite differently from the control of acute pain However, in either case it is important to give due consideration to the optimal dose and route of administration

The Optimal Dose—The optimal dose of a drug may be defined as that minimal dose that provides the desired therapeutic effects The importance of determining the optimal dose of narcotic in managing pain, whether it be acute or chronic, is obvious In the treatment of acute pain there is a premium on rapid and effective relief and there is little opportunity for leisurely trial-and error prescription Moreover, since drugs produce unpleasant and at times dangerous side effects, the flexibilities in dosage are not as great as is permissible with many other drugs, such as penicillin, for example In managing chronic pain the use of minimal effective dose reduces the risk of addiction

Influence of Pain Intensity—The optimal dose of each drug for the "average' patient has been mentioned in the discussion on pharmacology In determining the dose for a specific situation it is necessary to consider the age, weight, and physical status of the patient, the reflex irritability of his nervous system, the intensity of the pain, and the presence of coexisting disease However, except in extremes of age, the *intensity of pain is the most important factor determining the amount of analgesic required for relief* Since we possess no means of accurately assessing the severity, quality, and duration of clinical pain the careful history and observation of the patient and the patient's description of the symptoms remain the most important guides in pain management

Other Factors Influencing Dosage—In addition to estimating the intensity of pain, other factors must be considered Fever, like pain, increases the nervous reflex irritability and the metabolism of the individual, which in turn affects the intensity of pain Coexisting disease such as hyperthyroidism also causes increase in metabolism, and, therefore, a greater amount of analgesic has to be given to these patients for the relief of coexisting pain On the other hand, the dose must be decreased in patients with hypothyroidism, in those who are debilitated, and in the aged and infants

Evaluating the Effects of a Dose—It bears re emphasis that the analgesic action of morphine and its congeners is so selective that pain can be relieved in most cases with 10 mg or less of morphine or the therapeutic equivalent of other drugs All too often, larger amounts than necessary are prescribed, and consequently undesirable side effects occur, particularly respiratory depression

Following determination and administration of the initial dose, its efficacy should be carefully assessed by the same methods The widespread practice of

drug intravenously In this way the physician not only provides much needed relief promptly but is better able to judge the effects and the optimal dose for subsequent administrations For very urgent situations intravenous injections of alphaprodine (*Nisentil*) will provide more prompt relief than any other analgesic Inadequate relief 15 to 20 minutes after intravenous administration is an indication for an additional dose In the presence of *very severe pain it may be necessary to* administer several therapeutic doses at intervals of 15 to 20 minutes Under such circumstances the total dose of narcotic administered may be far greater than usually required but properly given it will not cause depression because the severe pain antagonizes the depressant effects of these drugs *An uncommon grievous* error is to deprive patients of the relief they may obtain from analgesics by administering them in routine fashion

VISCERAL PAIN —*The above comments* also apply to the control of severe pain associated with visceral disease Patients with excruciating pain of acute pancreatitis perforated peptic ulcer, severe renal or biliary colic, mesenteric thrombosis, or coronary occlusion may require up to 45 mg of morphine administered intravenously in 10 mg doses at intervals of 15 to 20 minutes In patients with renal colic it is important to be prepared to treat acute narcotic depression (page 229) because the pain may suddenly disappear should the calculus be passed

In patients with severe pain who are not adequately relieved with narcotics temporary interruption of the pain pathways with nerve blocking technique is indicated

Chronic Pain —The management of severe, intractable, chronic pain is a most difficult problem, often taxing the therapeutic skill of the physician to the utmost This is especially true in pain of undetermined origin, in which case there may be a tendency for the busy practitioner to take the easy way out and resort to addictive analgesics for a prolonged period Without doubt this can sometimes be one of the most serious, if not disastrous errors in clinical medicine The physician may be entrapped *into committing such an error by humane though ill considered decision* to keep the patient from suffering Administration of narcotics in patients with chronic pain is a frustrating short lived type of kindness such mistaken humanitarianism inevitably is nothing but a great disservice to the patient This is so because, with continued use of the addictive analgesics tolerance to the analgesic action develops and eventually an impasse is reached in which the patient s daily narcotic requirements are high, yet the alleviation of pain is inadequate In addition to being *medically unsatisfactory this situation is* fraught with the possibility of social and economic disaster for the addicted patient and his family

It is obvious that narcotic therapy is not the answer to the management of patients with chronic pain This is especially true of patients suffering from trigeminal neuralgia, glossopharyngeal neuralgia, causalgia, or other reflex dystrophy chronic visceral pain, 'idiopathic' neuralgia *severe pains due to chronic arthritis* headaches angina pectoris, and other severely painful disorders that otherwise do *not constitute an immediate* threat to the patient's life These patients deserve an intelligent appraisal and a systematic plan for relief which will conserve their physical, mental and moral resources Every other method of relieving pain should be exhausted before the patient is hopelessly abandoned to a *narcotic regimen* These measures include psychotherapy, sedatives and nonarcotic analgesics,

pruritus, and respiratory depression, the drug should be administered *slowly* and with caution It is best to dilute the analgesic drug to a total volume of 5 to 10 ml and take 3 to 5 minutes for the administration Following the injection of the first milliliter, the patient should be observed and questioned for unpleasant symptoms The physician should be careful to avoid suggesting them by making neutral inquiries

Treatment of Acute Pain —Proper control of severe pain consequent to surgical or accidental trauma or disease with narcotics requires discretion and clinical judgment garnered from experience It should be re emphasized that injury, whatever the cause or degree, is not necessarily followed by severe pain It is obviously essential to avoid routinization of narcotic therapy If any analgesic is indicated the optimal dose should be administered at irregular intervals and *not by the clock* Since dependence may result from as few as 1 or 2 injections of a narcotic if the injections are given to a person with special psychologic problems, these drugs should be discontinued as soon as severe pain subsides, and nonnarcotic analgesics should be substituted *Special caution should be exercised in administering drugs to* alcoholics, to patients who manifest extreme degrees of anxiety and overdependent attitudes toward the physician, to those with history of multiple operations, to individuals whose complaints are markedly out of proportion to the physical findings, and to patients with previous psychotic episodes

Postoperative Pain —Postoperative pain requires careful evaluation of the patient if proper use of narcotics is to be made because severe pain does not necessarily follow operations Approximately one fourth to one third of unselected patients in general surgical wards experience no significant postoperative pain The incidence of pain varies according to the patient, the site of operation, type of incision, etc Operations involving superficial parts of the body, extremities, head and neck are followed by much less pain than intra-abdominal or intrathoracic procedures Most patients who experience postoperative pain can be relieved with 10 mg of morphine or equivalent analgesic doses of other drugs administered subcutaneously If this dose proves inadequate, a similar dose is administered intramuscularly in 2 to 3 hours If this still proves ineffective, it is best to change to another drug

The intensity of postoperative pain usually diminishes progressively so that at the end of 48 hours it does not require narcotics This, together with the fact that duration of analgesic effects of narcotic drug varies among different individuals emphasize the importance of prescribing the drug in lower succeeding doses and only for relief of pain Since many of these patients experience discomfort related to anxiety, sleeplessness, apprehension, and nausea, the intramuscular injection of pentobarbital, 100 mg per 70 Kg, is a very useful adjunct to a narcotic for routine postoperative use Good nursing care will further enhance the effectiveness of analgesics The most important point to be made concerning postoperative pain is to avoid routine administration of narcotics at regular intervals

injury when their general condition may preclude adequate absorption of narcotics from under the skin In such cases it may be advisable to administer the analgesic

out divulging the amounts in each syringe This is done to avoid bias on her part One or two doses of placebo may also be included to ascertain the degree of placebo reaction The nurse is requested to observe and record accurately the results after each injection The *smallest dose that provides comfort with minimal side effects* is selected as the optimal dose Obviously this prolonged search for the optimal drug and optimal dose cannot be used in acute pain

In order to delay addiction and tolerance the narcotics should be given at irregular intervals It should be stressed that the patient should be given sufficient amounts of the drug and at intervals to obviate periods of severe pain One of the practices that makes psychologic dependence develop more quickly is failure to use enough of the drug to achieve the desired effects This situation can be avoided by assuring the adequacy of the dose and by giving the drug promptly on the appearance of pain and not waiting until the patient writhes with pain

The fear of pain and other affective reactions to pain may be modified by the use of drugs other than analgesics such as barbiturates, Thorazine and amphetamine

RATIONAL BASIS FOR NEW NARCOTIC ANALGESICS FOR THE RELIEF OF PAIN

Since 1803 when Sertuner discovered and isolated morphine from opium many clinicians have accepted and appreciated its virtues without much concern about the available laboratory and clinical evidence which indicates that this and other opiates have potentialities for harm However these disadvantages have been recognized by some clinicians pharmacologists and chemists a fact reflected in their zeal and ceaseless effort to produce a better analgesic resulting in the synthesis of hundreds of narcotics Serious consideration of what has been said in previous pages promptly indicates the need for better analgesics The ideal analgesic would have the following characteristics

1 It would produce satisfactory analgesia in at least 90 per cent of parenteral administrations and in 60 per cent of the oral trials

2 Its *side effects* would be minimal particularly upon respiration circulation and cerebration Administration to ambulatory patients would not be followed by untoward reactions

3 Since severe pain is in frequent association with spasm of smooth muscle it would have spasmolytic as well as analgesic action It would not be spasmogenic

4 Prolonged usage would not lead to tolerance habituation or addiction

5 Usefulness in patients regardless of the age or disease is desirable

6 It would be administrable by any route without irritation

7 It would be effective orally

8 Its physical properties would allow ease of preparation sterilization and storage without deterioration

NONANALGESIC DRUGS IN THE RELIEF OF PAIN

Hypnotics and Sedatives —Sedation may be of great value in reducing tension and thereby decreasing pain in some patients Since pain interferes with sleep many patients derive great benefit from drug induced rest and sleep The most

physical and roentgen therapy, analgesic blocks, and neurosurgical operations When this is done, there is some reasonable expectation that the patient may have actual freedom from pain as well as from the discomfort of pain

Since pain is both a sensory and an emotional experience, successful management needs to be directed simultaneously toward its several aspects At the same time, adjustments in the patient's life setting should be an intrinsic part of the therapeutic plan Provision for increase or decrease of physical activity, rest periods, combined with self administered physical therapy, simplification or increase of responsibility at work or at home, and exhaustive inquiry into the environment as a possible source of difficulty should be considered as part of the therapeutic plan for patients with chronic pain

By far the most important factor in the proper management of chronic pain is the performance of the physician If the physician views pain traditionally, merely as a symptom of physical disease, instead of considering the whole person, and further disregards the emotional changes that arise with pain, proper management is impossible Such a physician finds it necessary to administer narcotics frequently and, because he offers nothing else, tends to encourage the use of these drugs and make them essential to his patients On the other hand, the attentive physician, who offers his patients sympathetic understanding, kindness, cheerfulness, steady psychological support and realistic perspective, provides similar results without resorting to frequent use of addictive drugs He prescribes such drugs only as a specific part of the relationship between physician and patient and not as a substitute for that relationship

Patients with chronic pain who develop addiction as a consequence of prolonged narcotic therapy require equally competent management Notwithstanding the widely held belief that medically addicted patients should not be withdrawn from narcotics as long as the underlying painful illness remains, a serious attempt should be made to manage the pain in some other way and gradually discontinue the narcotics All of the above comments, of course, *do not apply* to patients with fatal illnesses, in whom the question of addiction is of little concern In patients with severe pain due to inoperable or recurrent carcinoma, the major concern of the physician is to provide relief not restoration to useful life

Determining the Best Drug —In patients in whom, either due to the nature of the disease or other circumstances, it is necessary to control severe chronic pain with narcotics the design for their use requires certain considerations Although morphine is the time honored drug, there are those for whom this drug fails For every patient who must be on a narcotic regimen in the face of intractable pain there is some opiate or opioid which is superior to any of the others Its supremacy depends upon complex qualities besides analgesia, and the final criterion in any case is which of the drugs best satisfies the patient His reaction to the drug represents a composite of analgesia, pleasant modification of mood, freedom from undesirable side effects and hang over, and many other things It is essential, therefore, to plan a systematic search for the most suitable drug This is best accomplished by the rotation system of administering a different drug every 24 hours and then having the patient decide which is the most effective

Determining Optimal Dosage —To do this, several different doses of the drugs are prepared in syringes which are coded and then given to the nurse with-

PHENOTHIAZINE DERIVATIVES —Chlorpromazine (Thorazine) and, more recently, *promethazine (Phenergan)* and promazine (Sparine) have been found to enhance the relief of moderate to severe pain due to a variety of disorders These drugs *significantly potentiate* the analgesic action of narcotics so that less of the latter drug needs *to be employed* The sedative and tranquilizing effect of Thorazine and, to a lesser degree, of Phenergan and Sparine eliminates the patient s anxiety *and tension*, causing him to view his pain with detachment, an action referred to as "pharmacologic frontal lobotomy"

For the relief of pain the phenothiazine compounds are usually employed in *conjunction with narcotics sedatives, or analgesics Oral or intramuscular administration* of 10 to 25 mg of Thorazine 3 times daily permits the reduction of narcotic doses to one half to two thirds those usually employed

Thorazine should not be used in patients who have received very large or unknown quantities of barbiturates, narcotics, or alcohol Because it potentiates hypotension produced by spinal or extradural anesthesia, it should not be used in conjunction with nerve blocks that produce extensive vasomotor paralysis The sedative and hypotensive effects limit the use of the phenothiazine compounds in ambulatory patients The physician should be on the alert for signs of jaundice, a complication which occasionally occurs following the administration of chlorpromazine

OTHER DRUGS —What has just been said regarding the combinations of analgesics with other agents can be applied to a heterogeneous group of drugs, which are frequently employed clinically in the management of pain

Amphetamine Benzedrine and other amphetamine compounds have been shown to enhance the analgesic effect of morphine and of nonnarcotic analgesics such as acetylsalicylic acid Moreover the amphetamine compound improves the mood and gives a feeling of well being, which in itself is important in the management of pain, particularly in chronic diseases The average dose of the amphetamine compound for such purposes is 2 5 to 5 mg

Scopolamine Because of its sedative and tranquilizing effects, scopolamine is frequently employed in combination with a narcotic agent in the management of pain, especially in patients who are restless and agitated The optimal dose in such cases is 0 3 mg

Miscellaneous Sedatives Chloral hydrate and other sedatives may be employed for the same purposes Thus 0 5 to 1 0 Gm of chloral hydrate with therapeutic doses of salicylates may be given 2 or 3 times daily to patients who have mild or moderate pain associated with anxiety, fear, and apprehension

PLACEBOS —Discussion of the use of placebos for the relief of pain belongs in this section because its effects are often very similar to those of sedatives and hypnotics Many careful clinical studies could be cited to emphasize the effectiveness of placebos in painful disorders and other subjective responses but one will suffice Beecher and his associates noted that fully one third of patients with severe, steady, postoperative wound pain were effectively relieved with saline or lactose placebos In a discussion on this subject, Beecher presents a summary of 15 publications containing many data substantiating the effectiveness of the placebos They are so potent that no physician can afford to ignore them

common drugs used for this purpose are the barbiturates, chloral hydrate, and the recently introduced phenothiazine compounds, Thorazine and Phenergan, and even alcohol In direct contradistinction to the analgesics, these have little, if any, effect upon pain perception but are used primarily because of their salutary modification of reaction or mood They will be considered briefly here and only in connection with their use in the relief of pain

BARBITURATES —Standard teachings have long suggested that in small hypnotic doses barbiturates are of little or no value in the management of pain In fact, these drugs have been considered contraindicated in the presence of pain because they produce restlessness and delirium These concepts probably developed as a result of laboratory studies which demonstrated that barbiturates fail to inhibit the perception of experimentally induced pain However, recent clinical studies on existing 'pathologic' pain have demonstrated the efficacy of hypnotic doses (100 mg) of pentobarbital (Nembutal) and secobarbital (Seconal) in relieving mild to moderate pain

The mechanism of their action is undoubtedly on the reaction phase of pain Barbiturates, like the opiates alter the psychic modification of pain In this manner, concern, anxiety, fear and significance are detached from pain In some patients in whom the psychic component of pain contributes greatly to the pain experience, the barbiturates alone may be sufficient to relieve the discomfort This is especially true in 'hypersensitive" or 'psychoneurotic" patients In some patients, discomfort is due to a combination of pain and apprehension and therefore a small dose of barbiturates should be employed as a supplement to a small dose of narcotics to achieve maximal benefit

Short acting barbiturates have the advantage of rapid effect and elimination, while the long-acting drugs may be used to establish a more or less sustained condition of hypnotic effect Restlessness in children who are having pain can frequently be controlled by small doses of 30 to 60 mg of phenobarbital

ALCOHOL —Imbibition of wine and other alcoholic beverages to relieve pain and produce euphoria dates back for centuries Alcohol in 5 to 10 per cent solution administered intravenously produces relief of mild to moderate pain through its euphoric effects by modifying the reaction to pain and, to a lesser extent, by raising the pain perception threshold By its cerebral effects, it also allays apprehension and eliminates fear and anxiety Thus it is conducive to mental and physical relaxation without producing depression of respiration or the other undesirable side effects inherent in narcotic therapy However, it is necessary to administer it under very close supervision Rate of flow needs to be carefully regulated, for otherwise the patient may become inebriated and consequently restless, overactive, and difficult to manage There is something to be said for oral administration of this agent

The intravenous administration of dilute (5 to 10 per cent) ethyl alcohol may be employed in the management of mild to moderate pain It is especially useful in geriatric patients in whom it is desirable to avoid the respiratory depression inherent in narcotic analgesics It may be combined with nonaddictive or addictive analgesics This method has been advocated for alleviation of the severe pain of angina pectoris and in cancer patients who otherwise require large doses of narcotics

NITRITES.—Nitrites relieve pain by relaxing smooth muscle through a direct (peripheral) action independent of innervation and without impairing the ability to contract on normal stimulation. Their most prominent action is on blood vessels of the coronary arteries.

XANTHINES.—Theobromine and theophylline and their salts and derivatives exert some relaxant effect on the smooth muscle of the tracheobronchial passages.

HISTAMINE.—The use of histamine in the management of pain is based upon the fact that it is a powerful vasodilator, being the most effective dilator of cerebral vessels. It has been found effective in histaminic cephalalgia and some cases of neuralgia. Following injection into a peripheral artery, it produces maximal vasodilation.

Ergotamine.—Ergotamine (Gynergen) has been employed in the management of migraine headache with some success. It is believed that ergotamine interrupts the mechanism of migraine by constricting overdistended arteries. The oral or sublingual dose is 4 to 5 mg. initially and 1 to 2 mg. every 1 to 2 hours until 10 mg. have been taken. The initial intramuscular or subcutaneous dose is 0.25 to 0.5 mg., which may be repeated in 1 to 2 hours if the headache is not relieved, but no more than 1 mg. should be administered in 24 hours. In order to minimize side effects, which include nausea and vomiting, muscular weakness, leg pains, numbness, and paresthesia, it is important to employ the smallest amount effective for relief. Moreover, in order to obtain prompt relief, it is necessary to give the drug during the prodromal stage.

Vasodilators.—These are discussed in Chapters 24 and 27.

Intravenous Procaine.—Intravenous administration of procaine and other local anesthetics for management of pain has passed the phase of enthusiasm and at the present time is not widely used. These drugs probably exert their effects on the central and peripheral nervous systems. This method may be tried in patients with intractable postherpetic neuralgia, pain of tabes dorsalis, and reflex dystrophies. It is essential to repeat the infusion every 3 to 15 days for a prolonged period of time.

Cobra Venom.—Cobra venom has been advocated for many years in treating chronic pain. A number of reports have been published with claims that this drug is effective in selective patients with certain types of pain. It has been suggested that this drug interferes with pain perception in the cerebrum although some believe that it has peripheral action. Despite the claims of most writers, this agent has proved ineffective in the hands of the writer and his associates. Because of equivocal results most clinicians have discarded its use.

REGIONAL ANALGESIC BLOCK

Regional analgesic block is a very effective method of producing a physiologic, reversible interruption of pain pathways. In the management of patients with

sidered in Chapter 13 on Anesthetics

Mode of Action The mechanism by which placebos relieve pain is not definitely known but probably involves the effects of suggestion on the reaction phase of pain In the previously cited study it was noted that the effectiveness of placebo was far greater when anxiety, apprehension, and mental stress associated with the pain were greater than when they were less There is also much objective evidence to support the thesis that the action of placebos is not limited to psychologic responses but also effects physiologic changes

Use Placebo is useful in the therapy of pain and other symptoms which have a predominant reaction phase It may also be used in dealing with neurotic patients and as an investigative tool to evaluate analgesics Of course, the effectiveness of the placebo depends a great deal on the physician, who unavoidably exerts a placebo effect merely by having been consulted professionally His personality, his actions, and his very attitude (including both conscious and subconscious elements) will greatly influence the direction and the magnitude of this psychotherapeutic effect If fundamental therapy is impossible or only partially effective, he may find it advantageous to supplement this personal placebo effect by the administration of placebo medication

There are two absolute requisites for success in the use of placebos the first is that the patient must believe he is being given a drug intended for the use of the relief of pain, and the second is that the nurse or attendant who administers the drug shares that belief A very effective way of prescribing a placebo is to include it in a series of doses of analgesics Provision of the nursing staff with already prepared solutions eliminates the natural prejudice against placebo which is rampant among those who do not appreciate the effectiveness of this therapeutic tool

ANALGESIA BY REVERSAL OF PAIN MECHANISM

There are a large number of drugs which relieve pain by acting directly on tissues or by mechanisms independent of the central nervous system They include the antispasmodics sympatholytic drugs, the spasmolytic drugs, and others Although these drugs do not fall within the scope of this chapter, their effectiveness in relieving some very severe forms of pain requires that they be briefly mentioned here They are of course considered in detail in appropriate chapters

Skeletal Muscle Relaxants —The recent widespread use of curare and other skeletal muscle relaxants in anesthesiology has naturally led to their use for the relief of pain consequent to muscle spasm such as seen in posttraumatic conditions arthritis poliomyelitis, tetanus, spastic states, and many other diseases The basis for their clinical use is their ability to produce selective paresis of the skeletal muscles by blocking motor impulses at the myoneural junction These drugs are discussed in Chapter 18

Smooth Muscle Relaxants —

ANTICHOLINERGIC DRUGS —Atropine and other anticholinergic drugs relieve spasm and excess motor activity of the smooth muscles and glands innervated by postganglionic cholinergic nerves These drugs are widely employed in disorders involving the gastrointestinal and urinary tracts Suitable doses diminish spasm and the associated pain and discomfort without interfering seriously with digestive processes

THE CHOICE OF AN ANESTHETIC

Joseph F Artusio, Jr, M D

THE CHOICE OF A GENERAL ANESTHETIC

INTRODUCTION

The general anesthetics used for the relief of pain during surgical operations are a little more than 100 years old They have stood the test of time well for some of the original agents are still in use

The primary purpose of general anesthesia is to render an individual unaware of the stimuli of environment, to provide freedom from pain, muscular relaxation and lack of memory for the experience It must be stressed that more important than the anesthetic is the choice of the administrator of the anesthetic The indications and the pharmacologic considerations of the drugs discussed in this chapter are indeed important bits of information However the physiologic upset to the patient that these anesthetic agents produce when well administered is minute in comparison with the physiologic upheavals that develop when the same agents are given by those who do not know how to deal with changes in ventilation and circulation that occur during surgical manipulation in the anesthetic state

CLINICAL APPLICATIONS AND PHARMACOLOGIC CONSIDERATIONS

Surgical Anesthesia Total unawareness of environment without the appreciation of pain or other sensory perception and without the memory of the experience —This degree of central nervous system depression is the most common form of pain relief in surgery today and is usually called the state of surgical anesthesia However this degree of central nervous system depression with its concomitant depression of ventilation and circulation is detrimental to the patient s homeostatic defense mechanisms It is gradually being replaced in many surgical centers by levels of minimal depression which are less injurious to circulation and ventilation

The 100 per cent potent anesthetic drugs are the ones best suited for this type of pharmacologic effect, ether, chloroform and cyclopropane being the most effective However because of the serious depression to cardiac function and peripheral circulation which occurs simultaneously with respiratory depression, chloroform is the least desirable of the three. Cyclopropane also produces this degree of central nervous system depression but, because it has little or no direct effect at the

SELECTED REFERENCES

Alexander, F A D Control of Pain, in Hale, D E Anesthesiology, Philadelphia, 1954,

Depression, Anesthesiology 16 674, 1955

Dripps, R. D, Millar, R A, and Kneale, D H A Comparison of Anileridine, Morphine,
& Obst 105 322, 1957

, and Jones, R E A Study of the Combina
ites for the Prevention of Respiratory Depres-
13 332, 1955

Analgetics, Springfield, Ill, 1955, Charles C
Thomas

Gruber, C M Codeine Phosphate, Propoxyphene Hydrochloride and Placebo, J A M A 164 956, 1957

Hardy, J D, Wolff, H G, and Goodell, H Pain Sensations and Reactions, Baltimore, 1952, Williams & Wilkins Company

Haugen, F P Current Concepts of the Pain Process, J Chron Dis 4 4, 1956

Isbell, H, and Fraser, H F Addiction to Analgesics and Barbiturates Pharmacol Rev 2 362, 1950

J A M A New and Unofficial Drugs 116 1481, 1958

Keats, A S Postoperative Pain Research and Treatment, J Chron Dis 4 72, 1956

Keats, A S, and Beecher, H K Pain Relief With Hypnotic Doses of Barbiturates and a Hypothesis, J Pharmacol & Exper Therap 100 1 1950

Keats A S, Telford, J, and Kurosu, Y Studies of Two New Potent Analgesics, Anileridine

Las ectiveness of Codeine and Meperidine
112 306, 1954

La of Morphine, J A M A 156 230,

Livingston, W K Pain Mechanisms New York, 1944, The Macmillan Co

Maurer, D W, and Vogel, V H Narcotics and Narcotic Addiction, Springfield, Ill, 1954, Charles C Thomas

Ripley, H S Psychologic Basis of Pain, in Bonica J J The Management of Pain, Philadelphia, 1953 Lea & Febiger

Starzl, T E, Taylor, C W, and Magoun, H W Collateral Afferent Excitation of Reticular

Secondary Anesthesia *Total* unawareness of environment, primarily used to produce a pharmacologic effect of the drug other than its effect on the central nervous system —This degree of central nervous system depression is provided as a result of inducing another pharmacologic effect with an agent which simultaneously produces general anesthesia For example, ether is administered to patients during a drug resistant asthmatic episode because it produces bronchial dilatation when given in doses which also depress the nervous system Such a dose will abort the attack of drug *resistant asthma but will carry with it the same dangers* as any other general anesthetic The risk is thought to be justified in view of the threats inherent in uncontrolled asthma At present ether is the best agent available for this pharmacologic effect The great threat to the patient during a convulsive episode apart from physical injury is the secondary effect of hypoxia and hyper capnia The respiratory musculature is contracted along with the other somatic muscles during a generalized convulsion whereas the pharmacologic effect sought of the anesthetic is relaxation of respiratory muscles In relaxing the muscle spasm by central depression the anesthetic agent allows the muscles of respiration to function and to provide respiratory gas exchange The great danger however is depression of the respiratory center by the anesthetic used to control the convul sion *In this situation* one must be prepared to treat apnea then the recurrence of the convulsion then apnea again etc until the cycle is broken The danger of respiratory depression can be adequately met with suitable apparatus to provide arti ficial ventilation The thiobarbiturates and the ethers are used successfully to con trol convulsions Here I think the agent of choice is the intravenous barb turate

THE SEVERAL DRUGS

Surgical Anesthesia

The potent or 100 per cent anesthetic agents are the ideal drugs to produce this level of depression However all except chloroform are explosive or flammable

Volatile Vapors —

Chloroform —Chloroform one of the most potent anesthetics in use today has a small margin of safety in that cardiac overdose occurs almost simultaneously with respiratory overdose Resuscitation from this agent may be extremely diffi cult because both systems are paralyzed Chloroform also sensitizes the heart to epinephrine arrhythmias hence one must not use epinephrine or norepinephrine with chloroform Liver damage with central necrosis of the liver lobule is well *described following* chloroform administration However, this degree of liver damage is probably caused in part by hypoxia associated with inadequate ventila tion during administration

Ether —Ether is ideal for this degree of depression It has a wide margin of safety in that the anesthetic dose *is approximately half that producing* respiratory arrest When respiration does stop because of a high concentration of ether in the brain circulation is still maintained for a period of time, so that resuscitation is usually successful The cardiac output during ether anesthesia is maintained primarily by ether s stimulation of adrenal medullary secretion *and the liberation* of sympathetic vasopressors by the cardiac sympathetic nerve endings If however

neuromuscular junction more profound central nervous system depression is required to provide large muscle relaxation with it than with ether Ether (ethyl ether) is still by far the best agent available today for this degree of anesthesia It is potent, has good peripheral blocking action at the neuromuscular junction, and is readily controllable

Analgesia Awareness of environment with sensory perception, but without the appreciation of pain and without the memory of the experience —This degree of central nervous system depression is comparable to the first stage of anesthesia of Guedel s classification and is sometimes called the state of analgesia Central nervous system depression of this degree can be tolerated by patients in the extremes of age those with cardiovascular disease the debilitated those with depleted blood volume from acute hemorrhage or contracted blood volume secondary to a chronic debilitating disease Where minimal central nervous system depression is maintained throughout a surgical procedure in such patients both the respiratory and circulatory systems withstand the stress without signs of decompensation so that they may be safely carried through extensive procedures

It was this level of anesthesia that was once thought to be dangerous to the patient permitting deleterious effects on the central nervous system by noxious stimuli The great fear of entering a delirium phase made the administrators of the anesthetic agents apprehensive of using this level of anesthesia for any but operations on the surfaces of the body and of extremely short duration but if one induces analgesia in retrograde fashion with ether so that the surgical stage is entered once in its lightest degree the delirium phase does not develop no matter how frequently the transition is made from a light level of depression to a deeper level of depression The only danger inherent in this level of anesthesia in which the patient can respond to questioning is the possibility of remembering the experience If there is some memory of the experience an extremely rare occurrence, it is however, recalled as an extremely pleasant experience and not one that was unpleasant or painful

The best available agents today for this type of depression I feel are ether nitrous oxide and ethylene in that order with or without the simultaneous use of a muscle relaxant

Amnesia Awareness of environment, with pain relief provided by another agent with no memory of the experience —This degree of central nervous system depression provides strong sedation during an operation performed under some form of regional anesthesia During long regional procedures the patient may become restless and fatigued and frequently may interpret pressure and traction as pain The anxiety and the misinterpretation of a stimulus as a painful one makes an excellent regional block inadequate

A hypnotic drug will induce a state in which the individual is partially or completely aware of environment but during which anxiety, restlessness and incorrect interpretation of the stimulus no longer exist and the operating conditions are better both for the surgeon and for the patient The pharmacologic effect is one of relaxation and freedom from worry It complements well performed regional anesthesia There is little or no danger the principle of light anesthesia obtains, so that the organism is not depressed by the anesthetic

weak anesthetic agent, as mentioned before apply to nitrous oxide in even greater degree *To produce even the lightest level of surgical anesthesia requires 80 to 90 per cent of this gas* The danger from hypoxia is indeed great

Nonvolatile Agents —

THIOBARBITURATES —The drug most commonly used is thiopental sodium (Pentothal Sodium) Although other thiobarbiturates have recently been introduced methitural (Neraval), *thiamylal (Surital) they have little or no advantage over* thiopental sodium These agents have little or no analgesic potency, and induction of a state of surgical anesthesia requires a large amount of the agent When they are used alone to induce this depth of depression, severe respiratory and circulatory depressions ensue Since the thiobarbiturates are fat soluble and are readily absorbed by the fat depots when large doses are used to *induce anesthesia there is* considerable fat storage The drug is released from fat maintaining the barbiturate blood level and prolonging anesthesia after its administration has been discontinued

Because of the profound effects on both circulation and ventilation and the fat storage, it is not wise to use these agents for this degree of depression

TRIBROMOETHANOL (AVERTIN) —This is another agent without analgesic potency It produces greater respiratory and circulatory depression at this level of anesthetic depression than the thiobarbiturates It is of no value for surgical anesthesia

HYDROXYDIONE (VIADRIL) —This steroid without hormonal properties has not presented any special advantages

Analgesia

Volatile Vapors —

CHLOROFORM —This extremely potent agent has really had no clinical trial for this form of anesthesia One could speculate, however, that because of its intense analgesic properties *chloroform might be the ideal agent This drug, therefore,* should be given a clinical trial for this degree of anesthesia

ETHER —Ether is established as the best agent for this degree of anesthesia There is both intense analgesia and amnesia with little or no disturbance to the cardiovascular or respiratory system

HALOTHANE —While this agent may be an excellent one for analgesia there is however insufficient trial at this level of nervous system depression

VINYL ETHER —Because of rapid action and rapid recovery vinyl ether is *difficult to control during this level of anesthesia Because of possible* hepatotoxic effects it is not wise to use it for prolonged operations

ETHYL CHLORIDE —For the same reasons as for vinyl ether, ethyl chloride is not a suitable agent with which to maintain a patient at this *level of anesthesia*

Gases —

CYCLOPROPANE —Because of the rapid recovery with this agent it is difficult to maintain a steady level of analgesia but high flow nonbreathing techniques may approach a constant analgesic state with this agent

NITROUS OXIDE —*If this weak analgesic is given* together with an apneic dose of a muscle relaxant a state can be developed which approximates the analgesic state It must be borne in mind however, that the total effect may be related to

there is adrenal insufficiency, ether may be a serious depressant to cardiac output from the very beginning of its administration

HALOTHANE (FLUOTHANE).—Halothane is an extremely potent agent, more potent than chloroform Cardiovascular depression is so severe during this degree of anesthesia when Fluothane is used as a sole agent that it should not be used for this level of central nervous system depression

VINYL ETHER.—Vinyl ether (Vinethene) is a potent agent with a rapid onset there is rapid recovery from its effects and it is of use for this degree of depression only for procedures lasting less than 30 minutes Used for a long period this agent has toxic effects on the liver which may become permanent It is important to note that during the early administration of this agent convulsive movements may be seen These are not asphyxial convulsions such as those that may be seen during diethyl ether administration but are manifestations of central irritative phenomena produced by the drug itself They are benign and do not have the importance of the convulsions related to asphyxia during ether administration

ETHYL CHLORIDE.—Ethyl chloride is a potent drug which produces rapid onset of anesthesia and is followed by rapid recovery It is used primarily as an inducing agent Its one drawback is its primary depressing effect on the heart, an action similar to that of chloroform The patient should always be well atropinized before the administration of this agent

TRICHLOROETHYLENE.—Although a potent agent trichloroethylene is an extremely poor one for this degree of anesthesia At this stage of depression primary effects on the respiratory mechanism may result in tachypnea and inadequate gas exchange Cardiac irregularities may also develop It should never be used in closed system anesthesia associated with alkaline carbon dioxide absorbing agents because under these circumstances it breaks down into the toxic dichloracetylene

Gases.—All available gases are explosive and inflammable except nitrous oxide which supports combustion

CYCLOPROPANE.—Cyclopropane a potent agent is an ideal drug for this level of anesthetic depression With it however one must be continually on guard against respiratory depression and respiratory acidosis Through its vagal action cyclopropane depresses the sinoauricular node so that simultaneously administered epinephrine may excite foci in the ventricle which may then dominate the cardiac rhythm Because of its potency there is usually present in the rebreathing mixture during closed system anesthesia oxygen in concentrations of at least 80 per cent Thus it is the best gas for this level of anesthesia

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trator increases the concentration of this agent, oxygen in the inspired mixture is sacrificed and the patient's central nervous system suffers from all the deleterious effects of hypoxia Thus the great danger from this anesthetic agent, where used for this purpose, lies in its lack of potency

NITROUS OXIDE.—Nitrous oxide is a weak inorganic gas, and because of its lack of potency it is an extremely poor one with which to produce surgical anesthesia. Nitrous oxide is a weaker anesthetic agent than ethylene All the dangers of a

HALOTHANE may be of value in reducing blood pressure during surgical procedures

TRICHLOROETHYLENE is of no value

VINYL ETHER can be used to control convulsions for the same reasons as ether

ETHYL CHLORIDE is of the same value as vinyl ether

Gases —

CYCLOPROPANE is not suitable

ETHYLENE is not suitable

NITROUS OXIDE is not suitable

Nonvolatile Agents —

THIOBARBITURATES are of importance in controlling convulsions, but one must be aware of the danger of apnea following cessation of the convulsion

AVERTIN is effective in controlling convulsions but severe respiratory and circulatory depression limit its value

A DESIGN FOR THE USE OF DRUGS FOR GENERAL ANESTHESIA

Surgical Anesthesia —The drugs used for this degree of depression are primarily the 100 per cent potent anesthetic agents Concomitantly they depress the central nervous system and the circulatory and respiratory systems In order to obtain the optimum anesthesia at this level one must carefully monitor the character of ventilation and its rate, the blood pressure, pulse quality, and heart rate and rhythm The care of each patient must be individualized When depressed to this degree there will be effects on both circulation and respiration in many, and if these are allowed to persist for even a brief period, death may ensue

Before the introduction of the skeletal muscle relaxants, this degree of depression was necessary for abdominal surgery However, because of the physiologic derangement produced by the concentration of anesthetic agent it was precarious to operate on extremely old patients and to permit this degree of depression to continue for long periods A modern concept is that surgical anesthesia should be induced to the lightest degree compatible with the surgical needs Peripheral muscle relaxation should not be produced by central action of these drugs and associated central nervous system depression but rather by the skeletal muscle relaxants

Analgesia —This degree of anesthesia appears to be the least disturbing physiologically It is a level of depression in which increasing numbers of anesthetics are being conducted for surgical procedures Analgesia can be accomplished with low concentrations of potent agents or high concentrations of weak anesthetic agents In either event at least 20 per cent of oxygen or more must be present in the inspired mixture at all times In those operations requiring muscular relaxation peripheral muscle relaxants should be given simultaneously with the anesthetic agent In procedures not requiring muscle relaxation, there is of course no such problem

Ether administered until the patient enters a level of depression in which he is unaware of environment and does not react to stimuli and then returned to awareness of environment, provides this light degree of depression satisfactorily

inability to move and amnesia for the experience Because of its weak analgesic potency and the possibility of breakthrough of painful afferent stimuli, this level of depression may be deleterious to the organism

ETHYLENE —Everything said previously for nitrous oxide applies to this agent

Nonvolatile Agents —

THIOBARBITURATES —As sole agents these are not valuable at this level of anesthesia They possess no analgesic properties and although a state of unawareness and amnesia can be produced the patient responds actively to all stimuli as well as to pain

TRIBROMOETHANOL (AVERTIN) —Tribromoethanol is of no value at this level of depression because of lack of analgesic potency

Amnesia

Volatile Vapors —

CHLOROFORM is of no value

ETHER is of no value

HALOTHANE is of no value

TRICHLOROETHYLENE is of no value

VINYL ETHER is of no value

ETHYL CHLORIDE is of no value

Gases —

CYCLOPROPANE is not suitable

ETHYLENE is not suitable

NITROUS OXIDE is not suitable

Nonvolatile Agents —

THIOBARBITURATES —These drugs are ideal for this type of psychic sedation To prevent appreciable fat storage of the drug one only has to see that the total dose of the drug is not large

TRIBROMOETHANOL —Avertin has ideal properties for this type of sedation However, it is too depressing to both circulation and respiration and, if used, would have to be given before the regional anesthetic

NARCOTIC ANALGESICS —These agents are only fairly effective for this type of depression They do not produce real sedation Although they will produce a type of euphoria in a large percentage of patients, dysphoria is common enough to make them undesirable

Secondary Anesthesia

The choice of the anesthetic agent used for this purpose depends entirely on the primary pharmacologic effect required of the anesthetic

Volatile Vapors —

CHLOROFORM is of little or no value

ETHER is ideal for patients in status asthmaticus for its bronchodilating effect The level of anesthesia must be relatively deep and of at least 30 minutes' duration Convulsions of a variety of types are controlled by the primary effect of ether to relax the respiratory muscles and to allow ventilation to become adequate

THE CHOICE OF A LOCAL ANESTHETIC

INTRODUCTION

With the introduction of the hypodermic syringe in 1853 by Alexander Wood and the demonstration of the anesthetic action of cocaine by Koller in 1884, adequate tools were available for the first time for the development of local anesthesia Halsted in 1884 and Corning in 1885 demonstrated the clinical value of cocaine for local anesthesia by the injection of this substance in various parts of the course of nerve trunks Since then many local anesthetics have been synthesized, largely in an attempt to reduce toxicity A discussion of the local anesthetic agents that follows will confine itself to those agents which are most widely used today

CLINICAL APPLICATIONS

The action of these drugs is to interrupt pain impulses in a specific region of the body Depending upon the clinical need, a nerve can be blocked in any portion of its course from its exit from the cord to its termination

Local Infiltration—Nerve endings in the skin and subcutaneous tissues are blocked by direct infiltration of the tissue itself With spread of the anesthetic agent throughout the tissue the nerve terminals are affected This type of nerve blocking which is commonly known as local anesthesia, is used principally for surgical procedures involving a small superficial area in the healthy adult patient In the patient who is considered a poor risk for other forms of pain relief it is also used for nerve block of deeper structures by direct infiltration

The dangers of this type of nerve block are primarily those of too much drug in too short a period of time, with high blood level and systemic effects Since this type of application of the drug usually requires fairly large volumes, it is important that the operator use the lowest concentration of the drug which blocks sensory perception A careful record of the amount of anesthetic agent should be made Since anesthesia is usually determined by the patient s response to pain one can inadvertently give enough anesthetic to produce toxic symptoms

Although most of the available local anesthetics can be used for local infiltration anesthesia, procaine (Novocain) is the most widely used Certainly it is one of the least toxic and best understood of the available agents Lidocaine (Xylocaine) has enjoyed some recent popularity but has slightly higher toxicity than procaine

Field Block—Field block setting up walls of anesthesia around an area, rather than direct infiltration, has lost a great deal of its previous vogue It requires somewhat more precise knowledge of the nerves entering the area than does local infiltration, but, if done well, it provides good anesthesia within the walls of the block

The therapeutic indications are the same as for local infiltration anesthesia in surface lesions Since the field block itself usually infiltrates deeper structures, one must be extremely careful of inadvertent intravenous injection which can produce sudden toxicity There is less danger, however, of giving too much anesthetic, because the field block is usually performed with a smaller total dose of drug than in local infiltration

It also can be accomplished with nitrous oxide and oxygen at concentrations of at least 60 per cent nitrous oxide and not exceeding 80 per cent nitrous oxide, with the simultaneous use of a muscle relaxant and hyperventilation

Amnesia —This extremely light level of depression, often called sedation is ideally provided by the barbiturates The thiobarbiturate, thiopental, is the best agent available today Effects can be maintained with thiopental by adjusting the concentration so as to induce the state without excitation and without untoward side effects The patient must be watched continuously to maintain the optimum therapeutic effect of blocking environmental stimuli and preventing anxiety The continuous drip is preferred

Secondary Anesthesia —The place for the use of an anesthetic agent for this purpose depends entirely on the primary pharmacologic objective This problem will be considered in detail in appropriate other chapters

RATIONAL BASIS FOR NEW DRUGS FOR GENERAL ANESTHESIA

Surgical Anesthesia —The drugs available for this purpose at present seem to satisfy the need on a pharmacologic basis However most of them are explosive and flammable a nonflammable nonexplosive drug of this potency is needed They would be ideal if onset and recovery were rapid If the new drugs used did not induce cardiac arrhythmias in the presence of epinephrine, they would have still another advantage over some now in use

It is my opinion however that this degree of central nervous system depression is no longer needed or desirable for most operations

Analgesia —At the present writing it appears that all one needs is to produce amnesia for the experience and analgesia for the painful stimuli arriving by affer ent pathways Total unawareness of environment and muscular relaxation pro duced by central depression are no longer necessary the state of analgesia may often provide the ideal anesthetic effect for both patient and surgeon

It is for this state of central nervous system depression however, that I feel there is the greatest room for improvement in new drugs The target is a non flammable nonexplosive drug sufficiently potent to induce amnesia and analgesia in concentrations of approximately 40 per cent of agent and 60 per cent oxygen Thus there would be 3 times ambient oxygen in the inspired mixture at all times Both assisted and controlled ventilation could be carried out vigorously at will without fear of drug overdose to the central nervous system, the circulation, or respiration Muscle relaxation would be provided by a peripheral muscle relaxant

Amnesia —Although the barbiturates are the ideal sedatives available today and the thiobarbiturates the most effective for anesthesia the latter have the draw back of fat storage so that their effects may not be eliminated for fairly long periods of time A drug is needed whose metabolism is more rapid than the now available thiobarbiturates and with little or no fat solubility, so that drug action will be terminated rapidly

Secondary Anesthesia—Where the therapeutic objective is not anesthesia, drugs whose pharmacologic effects are not associated with concomitant deep anes thesia would be desirable

The local anesthetics used in this fashion behave according to the phy principles of movement in a closed fluid system The use of a heavy solu termed a hyperbaric solution, or a light or hypobaric solution can, by the co positioning of the patient on the operating table, result in different areas of thesia While the anesthetic agent penetrates the nerve roots it also affects cord, but penetrates only its most superficial layers

The smaller unmyelinated fibers are anesthetized first and the large myelin ones later, so that blockade occurs first with sympathetic, then with the sens and finally with the motor fibers Recovery takes place in the reverse order

The great danger in this technique is the inadvertent injection of nox substances other than the conventional local anesthetics, such as, for example, contents of a mislabeled ampule or an anesthetic solution that has been conta nated during wet sterilization Trauma during the introduction of the needl another danger, destruction of an end artery to a segment of the cord may re in permanent disability Because this technique always produces sympath block in association with sensory and motor block spinal anesthesia in the up thoracic region is often associated with sharp falls in blood pressure These m be guarded against and treated by the judicious use of vasopressors An extrem high level of anesthesia may affect the medulla, so that immediate resuscitat measures are necessary to control the total spinal block Spinal analgesia sho never be performed in patients with a history of central nervous system disease or disease of the vertebral column

In situations in which the anesthesiologist feels that general anesthesia is co traindicated due to pre existing disease and provided it can be induced satisf torily without paralyzing vital function it is a technique that is safe and shou be encouraged

The local anesthetic agents to be preferred for this block are procaine tetracai (Pontocaine) or butethamine (Monocaine)

Topical Block —This type of block is accomplished by applying the anesthe agent to mucous membrane surfaces and in that way blocking the final nerve term nals in the mucosa The oral cavity, the pharynx larynx and tracheobronch tree provide surfaces for this type of nerve block It is often used to block sens tion and to interrupt reflex activity during bronchoscopy and other manipulatio of the respiratory tract

The great danger is associated with overdosage, often due to too rapid al sorption of the anesthetic To circumvent this danger one must use a fine spra low concentration of solution, and critical attention to total volume used at an one time In our hands Xylocaine (lidocaine) appears to be the best topic anesthetic, with Pontocaine, cocaine, and others nearly as satisfactory Procain is of little value because there is virtually no absorption from mucosal surfaces.

GENERAL PHARMACOLOGIC CONSIDERATIONS

Anesthetic Effect —These agents interfere with nerve transmission and al though there are many theories the exact mechanism of action is unknown Inti mate knowledge of the actual changes in the cell itself will be necessary before the

Peripheral Nerve Block.—This technique, commonly called regional anesthesia, places the local anesthetic agent in direct contact with the nerve The therapeutic applications of this type of block are many The nerve can be blocked at any portion of its peripheral distribution to induce an area of anesthesia from the site of block throughout the entire peripheral distribution of the nerve Frequently several nerves must be blocked to produce anesthesia of a part

Peripheral nerve block has value as a diagnostic or therapeutic aid in pain problems in most areas of the body Local anesthetics can also be used to block nerves of the autonomic system Thus peripheral nerve block can be used to dilate peripheral vessels which are constricted due to a sympathetic influence

Nerve blocks of this type require relatively small amounts of anesthesia and are relatively free of the danger of overdosage Greater danger is involved where the nerve to be blocked lies very close to blood vessels which can be entered or to closed cavities which can be inadvertently pierced The anesthetic agent should not be put into the nerve itself but rather around the nerve Intraneural injection invites neuroma formation

All of the available local anesthetic drugs can be used in this type of nerve block

Paravertebral Nerve Block—This blocks the entire distribution of the nerve after it leaves the intervertebral foramina The therapeutic applications of this block are primarily the same as for blocks in the peripheral portion of the nerve, and the same general dangers are presented However, since the block is performed in such close proximity to the subarachnoid space, large vessels and, in the thoracic region, the pleural space, the dangers are proportionately greater and the technique should be carried out only by skilled operators

Epidural or Caudal Block—Epidural block is usually the choice of an anesthesiologist who particularly likes the technique, but it also may be used to prevent the sharp drops in blood pressure that may develop after subarachnoid block It has been used recently to control postoperative pain

It is a rather difficult technique, one usually mastered only by the anesthesiologist It requires a large volume of solution, which increases the possibility of toxic reaction There is also the danger of inadvertent puncture of the subarachnoid space resulting in a massive spinal block

Caudal block is in essence an epidural block in the caudal region It has great application in pain relief for the obstetrical patient as well as for operations in the area of the rectum or genitalia

All of the available local anesthetic agents have been used in epidural block, and choice is a matter of one s personal preference and the desired duration of the block

Subarachnoid Block (Spinal Analgesia)—Subarachnoid block, commonly called spinal anesthesia but more correctly spinal analgesia, requires that the anesthetic agent be deposited within the subarachnoid space so that the anesthetic mixes with spinal fluid The anesthetic can be placed in this area in a single injection in which the total calculated dose is injected at that time, or, by the introduction of a malleable needle or spinal catheter, the drug may be introduced intermittently over long periods of time

The most intelligent way to treat this type of reaction if it is severe, is by direct cardiac massage The indications are that ventricular fibrillation is the primary cause of the circulatory collapse, and the only way to restore normal cardiac mechanism in this situation is by direct massage or defibrillation and shock therapy In minor cardiovascular reactions, in which moderate hypotension and bradycardia are the manifestations of the reaction, intravenous administration of vasopressor drugs such as Neo Synephrine, in doses of 1 mg, may be used to re store circulatory dynamics to normal

One can prevent these reactions or reduce their incidence by using the low est concentration of drug suitable for the desired effect with slow meticulous in jection and frequent aspiration The testing of these patients for sensitivity is of little value since even the serious reactions can occur from the small doses and concentrations used in the testing material

THE SEVERAL DRUGS

The Alcohols

The alcohol group of local anesthetics are little used today They are liquids which are partially soluble in water Phenol cresol menthol and benzyl alcohol comprise but a few belonging to the group By far the most commonly used are benzyl alcohol and phenol Benzyl alcohol a representative of this group of local anesthetics is an aromatic alcohol It is of extremely low potency Its greatest uses are topical application and in combination with procaine for prolongation of the action of the latter

The Esters

The Benzoic Acid Esters—Cocaine and piperocaine (Metycaine) are repre sentative of this group of compounds which are simple aromatic acids in linkage with amino alcohol

COCAINE—Cocaine, a colorless white powder with 3 times the potency of pro caine decomposes on boiling Today it is used primarily as a topical anesthetic in 4 to 10 per cent solutions Cocaine has vasoconstrictor properties however there is no difference in the intensity of vasoconstrictor action of 4 per cent and 10 per cent solutions since drug levels in the blood are the same after the appli cation of equal amounts of each to areas of similar size It is a frequent offender in producing the central nervous system type of reaction Cardiovascular collapse is also seen It can produce addiction It is probably the most widely used topical anesthetic today

PIPEROCAINE—Piperocaine (Metycaine) is slightly more toxic than procaine It is thermostable and may be boiled It is used primarily for infiltration and nerve block anesthesia

The Para-Aminobenzoic Acid Esters—

LOW SOLUBILITY—Benzocaine (ethyl aminobenzoate, Anesthesin) is suitable only for topical anesthesia It is frequently added to other solutions to prolong the effect It is of low potency and toxicity and is stable in an aqueous or oily solution

HIGH SOLUBILITY—

Procaine Procaine is used primarily for infiltration and nerve block anes

Intensity of Effect.—The intensity of the anesthesia produced depends on the molecular structure of the anesthetic agent and the size of the nerve fiber in the area of application of the drug. The small unmyelinated fibers of the autonomic system and the small unmyelinated sensory fibers are the most susceptible because, unimpeded by myelin sheathes or dural coverings, the anesthetic agent can more readily penetrate fibers of this size. The larger sensory fibers are next affected, while the large myelinated motor fibers are affected last. It is possible to block nerve fibers differentially by adjusting the anesthetic concentration so that the block is limited to fibers of particular size.

Duration of Action.—The duration of a local anesthetic blockade depends upon many of the factors that are inherent in the intensity of action: the drug itself, the fiber size, and the area blocked, but most especially the concentration of anesthetic agent used in the area. Blockade of large motor fibers is of short duration, while blockade of small unmyelinated sympathetic fibers is of relatively long duration.

One way to prolong infiltration, peripheral nerve block, or spinal anesthesia is to inject a vasoconstrictor with the anesthetic. Since the latter slows the rate of absorption of the anesthetic, its effects are prolonged. Vasoconstrictors are of especial value along these lines in highly vascular areas. However, vasoconstrictors are not effective in retarding absorption from mucous membranes.

Toxic Reactions.—The toxic effects of anesthetic agents are intimately related to the concentration of the anesthetic agent in the blood stream. Common causes of high blood concentration are rapid absorption, concentrated solutions, and large volume of low concentration. Inadvertent injection of anesthetic agents into blood vessels and highly vascular areas also produces the systemic toxic reactions. High local concentrations of these anesthetic drugs not only increase the probability of systemic toxicity but also may produce localized nerve damage or necrosis of surrounding tissues.

The systemic toxic reactions are usually of two distinct varieties, a central irritative phenomenon followed by depression, the other by cardiovascular collapse.

Central Reaction.—The central reaction is usually associated with high concentrations of anesthetic in the circulation. It is marked by irritability, talkativeness, and apprehension and may be followed by gross tonic and clonic convulsions and then depression followed by death. In other instances there may not be an excitation phase, only depression. One should be wary of the patient who suddenly becomes extremely sleepy following injection of a local anesthetic, because he may shortly become comatose.

The most effective regimen of treatment for the excitation type of reaction is to stop the injection of the anesthetic agent immediately and to use a rapid acting barbiturate, such as thiopental, intravenously, to control the convulsions. Because the barbiturate itself may also induce apnea, one must be prepared for artificial ventilation as well as treatment of a repetition of central irritation.

Circulatory Collapse.—The primary circulatory reaction is most difficult to treat, and accounts for most of the deaths due to local anesthesia. It may be seen during injection of minute amounts of anesthetic agent: suddenly the patient collapses, and usually before any resuscitative measures can be applied the patient is dead.

TETRACAINE (PONTOCAINE) is of no value

BUTETHAMINE (MONOCAINE) is useful in 0 5, 1, and 2 per cent solutions In 0 5 per cent solution the maximum dosage is 200 ml in 1 per cent solution the maximum dosage is 100 ml , in 2 per cent solution the maximum dosage is 50 ml.

LIDOCAINE (XYLOCAINE) is useful in 1 per cent solution with a total dosage of 50 ml It has excellent spreading power

Field Block —

BENZYL ALCOHOL is of no value

COCAINE is of no value

PIPEROCAINE is useful in 1 per cent solution with a maximum total volume of 75 to 100 ml

ETHYL AMINOBENZOATE is of no value

PROCAINE is extremely useful in 0 5, 1, and 2 per cent solutions In 0 5 per cent solution the maximum dosage is 200 ml , in 1 per cent solution the maximum dosage is 100 ml in 2 per cent solution the maximum dosage is 50 ml It is extremely effective and has a duration of 1 hour

CHLOROPROCAINE (NESACAINE) is useful in 1 to 2 per cent solutions

TETRACAINE is of no value

BUTETHAMINE is useful in 0 5, 1, and 2 per cent solutions In 0 5 per cent solution the maximum dosage is 200 ml , in 1 per cent solution the maximum dosage is 100 ml , in 2 per cent solution the maximum dosage is 50 ml

LIDOCAINE is useful in 1 per cent solution with a total dosage of 50 ml It has excellent spreading power

Peripheral Nerve Block —

BENZYL ALCOHOL is of no value

COCAINE is of no value

PIPEROCAINE is useful in 1 5 per cent solution with a maximum dosage of 50 ml

ETHYL AMINOBENZOATE is of no value

PROCAINE is extremely useful in 2 per cent solution with a maximum total dosage of 50 ml Duration of action is 1 hour The usual dose is 2 to 5 ml at each nerve site

TETRACAINE is slightly useful in 0 1 per cent solution with a total maximum dosage of 75 ml

BUTETHAMINE is useful in 1 per cent solution with a dose of 5 ml at each nerve site

LIDOCAINE is useful in 2 per cent solution with a maximum volume of 30 ml It has excellent spreading power Caution must be used in nerve block in the cervical region to prevent the spread of the anesthetic agent and involvement of the recurrent laryngeal nerve, resulting in vocal cord paralysis

Paravertebral Block —

BENZYL ALCOHOL is of no value

COCAINE is of no value

PIPEROCAINE is useful in 1 5 per cent solution with a maximum dosage of 50 ml

ETHYL AMINOBENZOATE is of no value

PROCAINE is extremely useful in 2 per cent solution with a maximum total

thesia and is of little value as a topical anesthetic It is an anesthetic of low toxicity Today it is the most widely used infiltration anesthetic It is a stable compound and may be boiled or autoclaved

Chloroprocaine (Nesacaine) Chloroprocaine is used primarily for infiltration and nerve block anesthesia but is also used for epidural and caudal block Its toxicity is about the same as procaine

Tetracaine Pontocaine (tetracaine, amethocaine) is an agent of high potency and high toxicity, 10 times that of procaine It is used principally for infiltration and nerve block anesthesia but it is also an effective topical anesthetic Its duration of action is about twice that of procaine It may be boiled or autoclaved

Butethamine Monocaine (butethamine) is used for infiltration and nerve block anesthesia It is slightly more potent than procaine It is stable and may be boiled or autoclaved It is little different from procaine in toxicity or use, but with perhaps some slight increase in duration

Miscellaneous Local Anesthetics

Quinoline Derivatives —

Dibucaine —The one anesthetic agent of value in this group of compounds is dibucaine (Nupercaine) It is the most potent and the most toxic of the local anesthetic agents in common use today It is 15 times as potent and toxic as procaine Duration of action is approximately 3 times that of procaine It is a stable compound which may be boiled or autoclaved It is used primarily for infiltration and regional block anesthesia and as a topical anesthetic Having lost a great deal of its vogue in spinal anesthesia, it is used now primarily with glucose for anesthesia of the perineal region

The Amino Acryl Amides —

Lidocaine —Lidocaine (Xylocaine) is the most recently introduced popular local anesthetic It is used primarily for infiltration nerve block anesthesia (other than the intrathecal route), and for topical anesthesia It has a high spreading factor so that it spreads over a fairly wide area following injection in tissue Its potency and toxicity are slightly greater than procaine It is a stable compound which can be boiled or autoclaved

THE RELATIVE MERITS AND USES OF SOME LOCAL ANESTHETICS

Local Infiltration —

Benzyl Alcohol is of no value

Cocaine is of no value

Piperocaine (Metycaine) *is useful in 1 per cent solution* with a maximum total volume of 75 to 100 ml

Ethyl Aminobenzoate is of no value

Procaine (Novocain) is extremely useful in 0 5, 1, and 2 per cent solutions In 0 5 per cent solution the maximum dosage is 200 ml, in 1 per cent solution the maximum dosage is 100 ml in 2 per cent solution the maximum dosage is 50 ml It is extremely effective and has a duration of 1 hour

Chloroprocaine (Nesacaine) is useful in 1 to 2 per cent solutions

COCAINE is used in a 2 to 10 per cent solution and provides excellent topical anesthesia *with rapid* onset and duration of action of about 1 hour The total application for topical use should be limited to 1 to 2 ml of a finely nebulized solution

PIPEROCAINE is useful in 3 per cent solution, but it is rarely used and is not as effective as lidocaine, Pontocaine, and cocaine

ETHYL AMINOBENZOATE is useful primarily as a 5 per cent ointment, it produces surface anesthesia for as long as it remains in contact with the area

PROCAINE is of no value

TETRACAINE is of value in 2 per cent solution with a total dosage confined to 1 ml Systemic toxic reactions are common It should be finely nebulized

BUTETHAMINE is of no value

LIDOCAINE is excellent used in 2 per cent' solution It has a rapid onset and *a duration of 1 to 1½ hours It has a good spreading factor It should be finely* nebulized

RATIONAL BASIS FOR NEW LOCAL ANESTHETICS

The drugs available at present for infiltration, nerve block, and spinal anesthesia *of short duration satisfy the needs of the therapeutic situation The search should continue, nevertheless, for local anesthetics of lower toxicity than procaine* In the topical anesthetics there is considerable need for decreased toxicity

The greatest need is for a local anesthetic with effects of long duration—days, weeks, months The available compounds and mixtures of compounds that are recommended for local anesthesia of long duration also have extremely high local toxicity Neurolysis with slough and necrosis of the surrounding tissues occurs If the anesthetic agent is placed in the vicinity of the spinal cord, and such an effect develops, partial or complete transection of the cord, with permanent paralysis, may follow An agent with low tissue and general toxicity as well as prolonged effect would solve the problems of the control of chronic pain, from whatever etiology, which, at the present time we can relieve only by agents which destroy the nerve tissue

SELECTED REFERENCES

General Anesthetics

Artusio, J A Quantitative Study of D tubocura rin (Flaxedil) and a Series of Tri Methyl an Anesthetized Man, Ann New York Ac

Artusio, J ailed Description of the First Stage of Et xper Therap *111* 343, *1954*

Artusio, J F, Jr Ether Analgesia During Major Surgery, J A M A 157 33, 1955

Beecher, H F, Francis, L, and Anfinsen, C B Metabolic Effects of Anesthesia in Man I Acid Base Balance During Ether Anesthesia, J Pharmacol & Exper Therap 98 38, 1950

Brewster, W R, Jr, Isaacs, J P, and Waino-Anderson, T Depressant Effect of Ether on Myocardium of the Dog and Its Modification by Reflex Release of Epi and Norepinephrine, Am J Physiol 175 399 1953

Bunker, J P, Beecher H K, *Brizzo*, B D, Brewster, W R, and Barnes, B A Metabolic Effects of Anesthesia II A Comparison of Acid base Equilibrium in Man and in Dogs During Ether and During Cyclopropane Anesthesia, J Pharmacol & Exper Therap 102 62, 1951

dosage of 50 ml Duration of action is 1 hour The usual dose is 2 to 5 ml at each nerve site

CHLOROPROCAINE (NESACAINE) is useful in 1 to 2 per cent solutions

TETRACAINE is slightly useful in 0 1 per cent solution with a total dosage of 75 ml

BUTETHAMINE is useful in 1 per cent solution with a dose of 5 ml at each nerve site

LIDOCAINE is useful in 2 per cent solution with a maximum volume of 30 ml It has excellent spreading power Caution must be used in nerve block in the cervical region to prevent the spread of the anesthetic agent and involvement of the recurrent laryngeal nerve resulting in vocal cord paralysis

Epidural or Caudal Block —

BENZYL ALCOHOL is of no value

COCAINE is of no value

PIPEROCAINE is useful in 1 per cent solution with a maximum dose of 75 ml

ETHYL AMINOBENZOATE is of no value

PROCAINE is useful in 2 per cent solution with a maximum total dosage of 50 ml

CHLOROPROCAINE (NESACAINE) is useful in 3 per cent solutions

TETRACAINE is slightly useful in 0 1 per cent solution with a maximum dose of 75 ml

BUTETHAMINE is slightly useful in 1 per cent solution with a total dosage limited to 75 ml

LIDOCAINE is very useful in 1 5 per cent solution with a dosage of 30 ml Extreme care must be used not to exceed the recommended total dosage

Subarachnoid Block —

BENZYL ALCOHOL is of no value

COCAINE is of no value

PIPEROCAINE is useful in 5 per cent solution, for low spinal, 50 mg, and for high spinal, 100 mg maximum dosage

ETHYL AMINOBENZOATE is of no value

PROCAINE is extremely useful in 50 to 200 mg maximum total dosage depending upon the level of anesthesia For low spinal, 50 to 100 mg, and for high spinal, 150 to 200 mg Duration of action is 1 hour

CHLOROPROCAINE (NESACAINE) cannot be recommended for use in this category at this time because of insufficient data

TETRACAINE is useful in total dosage of 5 to 20 mg It is usually given in hyperbaric solution weighted with glucose one half anesthetic agent and one half 10 per cent glucose It is advisable to limit total dosage to 14 mg, for low spinal 5 mg, and for high spinal 12 mg It is slower in onset than procaine and duration of action is 2 to 3 hours

BUTETHAMINE is useful It is similar to procaine Maximum total dosage for low spinal, 50 mg, and for high spinal 100 to 125 mg

LIDOCAINE is of no value

Topical Block —

BENZYL ALCOHOL is used in 4 per cent solution but lidocaine, Pontocaine and cocaine are more useful and more effective

THE CHOICE OF SEDATIVES AND TRANQUILIZERS IN GENERAL MEDICAL PRACTICE

Dale G Friend, M D, and
James T. Hamlin, III, M.D

INTRODUCTION

The concept of bringing about a calm or more tranquil mental state without any considerable degree of sedation is of recent origin although certain drugs which do this have been used in medicine for several centuries

The antihistamine promethazine (Phenergan) was early noticed to possess the ability to calm excited emotional states Although it produced some sedation, it did not behave like a sedative, since, when it was given in toxic amounts, it did not increase sedation but rather, if the dose was large enough, caused convulsions It was also observed that diphenhydramine (Benadryl) possessed somewhat similar sedating properties Many careful observers noted that these antihistamines seemed to exert their action more at the hypothalamic rather than at the cortical level It was also apparent that cortical activity was unimpaired although relaxation and calming of emotional tension was obtained

As a result of these observations a definite attempt was made to find more effective agents with similar properties The antihistamines, sedatives, and many other agents were carefully explored It is interesting to note that, in spite of the intense search, only one natural product exhibiting this type of action has been found This was *Rauwolfia serpentina,* a drug which had been in use as a tranquilizer for centuries in India

Analogues of promethazine were prepared and the phenothiazine series soon supplied most of the more effective tranquilizing drugs The search for more active antihistamines led to the discovery of the diphenylmethanes, a less potent class of agents than the phenothiazines Mephenesin, a weak irregular acting agent, supplied the stimulus that led to the preparation of the more effective propane and butanediol compounds The barbiturates and other sedatives, especially those exhibiting weak sedative properties, and the more potent sedatives, given in small doses, also have been added to the list of agents useful as tranquilizers Several chemically unrelated agents exhibiting tranquilizing action have been found recently and added to the list As a result of all this activity there are now nearly

Burnett, C H, Bloomberg, E L, Shotz, G, Compton, D W, and Beecher, H K A Comparison of the Effects of Ether and Cycloproprane Anesthesia on Renal Function of Man, J Pharmacol & Exper Therap 96 380, 1949
Fairlie, C W, Barass, T P, French, A B, Jones, C M, and Beecher, H K Metabolic Effects of Anesthesia in Man IV A Comparison of the Effects of Certain Anesthetic Agents on the Normal Liver, New England J Med 244 615, 1951
French, A B, Barass, T P, Fairlie, C S, Bengle, A L, Jr, Jones, C M, Linton, R R, and Beecher, H K Metabolic Effects of Anesthesia in Man V A Comparison of the Effects of Ether and Cyclopropane Anesthesia on the Abnormal Liver, Ann Surg 135 145, 1952
Habif, D J, Papper, E M, Fitzpatrick, H F, Lawrence, P, Smythe, C M, and Bradley, S E The Renal and Hepatic Blood Flow Glomerular Filtration Rate and Urinary Output of Electrolytes During Cyclopropane, Ether and Thiopental Anesthesia Operations and the Immediate Post-operative Period Surgery 10 241, 1951
Hershey, S G, Zweifach, B W, and Rovenstine, E A Effects of Depth of Anesthesia on Behavior of Peripheral Vascular Bed Anesthesiology 14 245, 1953

Local Anesthetics

Arrowood, J G, and Sarnoff, S J Differential Spinal Blocks, Anesthesiology 9 614 1948
Campbell, D, and Adriani, J Absorption of Local Anesthetic Drugs, J A M A 198 873, 1958
Geddes, I C Studies With Local Anesthetics, Brit J Anaesth 27 609, 1955
Hirshfelder, A D, and Bieter, R N Local Anesthetics, Physiol Rev 12 190, 1932
Loyd, J B The Chemical Structure and Nomenclature of Local Anesthetics, Brit J Anaesth 27 286, 1955
Steinhaus, J E Local Anesthetic Toxicity, Anesthesiology 18 275, 1957
Vandam, L D, and Dripps, R D Long Term Follow up of Patients Who Received 10 098 Spinal Anesthetics, J A M A 161 586, 1956

Table 13

Drug	*Usual Individual Dose*	*Usual Total Daily Dose*
Rauwolfia		
Crude drug (Raudixin)	50 100 mg	100 200 mg
Purified extract (Rauwiloid)	2 4 mg	2-4 mg
Reserpine	0 1 0 25 mg	0 25 2 mg
Deserpidine (Harmonyl)	0 1 0 25 mg	1 3 mg
Rescinnamine (Moderil)	0 25 mg	0 25 0 5 mg
Syrosingopine (Singoserp)	1 mg	1 3 mg
Phenothiazines		
Chlorpromazine (Thorazine)	10, 25, 50, 100, 200 mg	100 300 mg
Fluphenazine (Permitil)	0 25 5 mg	0 75 30 mg
Mepazine (Pacatal)	25, 50, 100 mg	100-400 mg
Methoxypromazine (Tentone)	10 50 mg	30 1500 mg
Perphenazine (Trilafon)	2, 4 8, 16 mg	8-64 mg
Pipamazine (Mornidine)	5 10 mg	15 30 mg
Prochlorperazine (Compazine)	5 10 mg	20-40 mg
Promazine (Sparine)	10, 25 50, 100, 200 mg	100 400 mg
Promethazine (Phenergan)	12 5 25 mg	25 50 mg
Thioperazine (Vontil)	0 5 1 mg	2 8 mg
Thioridazine (Mellaril)	10-100 mg	50-800 mg
Thiopropazate (Dartal)	5 10 mg	15 30 mg
Trifluoperazine (Stelazine)	2 5, 10 mg	6 20 mg
Triflupromazine (Vesprin)	20 100 mg	75 300 mg
Trimeprazine (Temaril)	2 5 5 mg	10 30 mg
Propanediols and Butanediols		
Carisoprodol (Soma)	0 35 1 Gm	1 Gm
Meprobamate (Equanil Miltown)	0 2 0 4 Gm	0 8 1 6 Gm
Phenaglycodol (Ultran)	0 2 0 3 Gm	0 6 0 9 Gm
Diphenylmethanes		
Azacyclonol (Frenquel)	20 100 mg	60 300 mg
Benactyzine (Suavitil, Phobex)	1 mg	4 16 mg
Captodiamine (Suvren)	50 100 mg	300-400 mg
Hydroxyzine (Atarax, Vistaril)	10, 25 100 mg	75 400 mg
Sedative Hypnotics		
Butabarbital (Butisol)	15 30 mg	60 120 mg
Ethchlorvynol (Placidyl)	100 200 mg	200 600 mg
Glutethimide (Doriden)	0 25 Gm	0 75 1 Gm
Mephobarbital (Mebaral)	30 100 mg	90-400 mg
Methyprylon (Noludar)	50 100 mg	50-400 mg
Phenobarbital	15 30 mg	60 120 mg
Others		
Ectylurea (Nostyn)	150 600 mg	0 6 2 4 Gm
Oxanamide (Quiactin)	400 mg	0 4 1 6 Gm
Phenyltoloxamine (Bristamine,	50 mg	150 200 mg
Histionex)		
Chlormezanone (Trancopal)	100 mg	100 300 mg

some residuals of its action may be present several days after the drug has been discontinued *In view of its* slow onset of action many prefer to give larger oral doses initially and reduce the dose once the desired effect is established In situations such as hypertensive encephalopathic crises or extreme excitement and agitation, the drug may be given intramuscularly in doses of 2 5 to 5 mg every 8 hours until the desired effect is secured Because of its mode of action and elimination it is not necessary to give slow release forms of medication

Effects —The effect of reserpine on the human organism is to bring about a peaceful tranquil state where the individual develops much less emotional response to situations about him Much of the emotional content, although recognized is

three dozen drugs recommended and being used as tranquilizers These agents are second only to the antibiotics as the most commonly prescribed drugs, one out of three prescriptions is for tranquilizers and they continue to increase in popularity

Although the term tranquilizer is in widespread use and seems to have general acceptance for this class of agents it is not entirely satisfactory Various other terms such as ataractic drugs and phrenotrophic depressants have been recommended but these have not received widespread acceptance Until there is better understanding of the mechanism of action and more selective criteria as to activity and function of these drugs the general term tranquilizer is useful as a descriptive term

It is indeed surprising to see how quickly this group of drugs has developed into the second most commonly used medicine in the brief span of approximately 6 years Unquestionably they are supplying an essential need in therapy Since this is the case it is important that agents for use in this category be selected and used wisely In order to do this it is necessary to understand the pharmacology of each class and to be aware of the untoward effects inherent in their use or produced as a result of improper administration or selection Table 13 lists by groups most of the available agents and gives the recommended dose

PHARMACOLOGY, TOXICOLOGY, AND CLINICAL USE

In order to discuss these basic actions of the tranquilizers it is necessary to separate them into different categories Members of the same group of agents behave in much the same general manner differing mainly in dose degree of selectivity of action and undesirable and toxic effects

Rauwolfia Materials—This group consisting of rauwolfia and its derivatives has supplied some of the most potent desirable and versatile of the tranquilizers In addition to the crude drug there is the semipurified alkaloid the purified alkaloid reserpine and three derivatives of reserpine, deserpidine (Harmonyl) rescinnamine (Moderil) and syrosingopine (Singoserp) Since reserpine the purified crystalline derivative of *Rauwolfia serpentina* is for the most part representative of the action of the entire group it will be discussed in detail Where there are significant exceptions these will be indicated

Mode of Action Reserpine has been shown to release bound 5 hydroxytryptamine from tissues and it in turn is metabolized to 5 hydroxyindole acetic acid and exceted in the urine It is thought by some that much, if not all of the action of reserpine is brought about by its altering the 5 hydroxytryptamine content in the brain by releasing it in excess amounts or by lowering its total content in the brain perhaps by interfering with binding sites or by inhibition of ATP coupled serotonin transport system This is an attractive theory and there are many things to support it but some observations such as reserpine s effect on brain norepinephrine and the action of other drugs which give similar effects but which do not alter the brain s 5 hydroxytryptamine content cannot be explained by it Obviously the whole story has not been unraveled as yet

Absorption Reserpine is readily absorbed but is a slow acting drug when given orally It may take several hours or if the dose is small a few days to build up its maximum effect Once in the body its effect is very slowly reversed and

There are many medical uses of reserpine and its derivatives It is excellent in controlling *agitated, tense, anxious*, psychoneurotic behavior Frequently it calms agitation created by drug withdrawal The excitement, agitation and delirium of alcohol withdrawal is rendered less acute by *reserpine Its chief use is in the* management of the hypertensive patient The reduction in blood pressure, brady cardia, and the relaxed mental state created by the rauwolfia drugs makes them without doubt the most versatile and useful agents for this situation It stimulates appetite and has been used successfully in the treatment of malnutrition Because of the nasal stuffiness, appetite stimulation, bowel overactivity, and tendency to produce mental depression, it is not as desirable an agent in the treatment of mild psychoneurotic behavior, *tension states, anxiety, and agitation as other members of* the tranquilizer series The phenothiazines or small doses of the sedatives, such as phenobarbital, are sometimes preferable in such cases

Phenothiazine Derivatives —There are at present 15 drugs in use in this series and new ones are added to it continually They vary from the comparatively weak promethazine and mepazine to the highly potent chlorpromazine (Thorazine), methoxypromazine (Tentone), prochlorperazine (Compazine), thiopropazate (Dar tal), *perphenazine (Trilafon), triflupromazine (Vesprin), trimeprazine (Temaril)*, and trifluoperazine (Stelazine) They are all derivatives of phenothiazine, and most have similar actions They all cause sedation in varying degrees Although most have some antihistaminic effect, this is of little significance except for promethazine, which is a potent antihistamine They exert some action against the catechol amines, epinephrine and norepinephrine, since they reduce the pressor effect of these substances Although these agents produce a similar central nervous system response to that seen with reserpine, they do not affect *the brain content* of 5 hydroxytryptamine

Action and Effects —The phenothiazines exert so many actions in the or ganism that at present it is impossible to postulate any basic concept of their action They potentiate and prolong the action of sedatives, narcotics, and anesthetic drugs they exert a potent antiemetic effect by virtue of a selective action on the chemoreceptor cells of the central emetic trigger mechanism and to a much lesser extent on the emetic center itself, and the central *heat regulating mechanism is* interfered with, leading to a breakdown in the control of heat loss and conserva tion *Trimeprazine* exerts a pronounced antipruritic effect Chlorpromazine exerts an antiarrhythmic action on the heart in certain circumstances, and ortho static hypotension is observed after the administration of chlorpromazine and closely related drugs

All the phenothiazines are capable of producing an obstructive jaundice, which is usually readily reversible when the *drug is discontinued Approximately* 2 per cent of patients given chlorpromazine will develop jaundice Jaundice has oc curred with prochlorperazine, but the incidence is so low that it is not a problem Agranulocytosis is reported in about 1 in 10,000 or more patients given chlorproma zine, but as yet none has been observed with the newer highly potent agents How ever, agranulocytosis must always be considered, and it is *the most serious com* plication of the use of the phenothiazines Higher doses of chlorpromazine pro duce *central nervous system changes characteristic* of parkinsonism The more potent perphenazine and prochlorperazine also exhibit considerable extrapyramidal

not felt so intensely and does not elicit the usual response For example, fighting fish no longer fight, hostile, aggressive, or frightened monkeys are no longer a problem but can be handled with ease and behave as though without fear or irritation Rats taught conditioned reflexes lose their conditioned response and revert to the original less desirable degree of responsiveness

Although patients receiving reserpine sleep better, relax better, and can go to sleep more readily, they do not exhibit much in the way of sedation They can perform normally and are easily aroused even though they have been given huge doses of the drug It increases gastrointestinal motility and the secretion of stomach hydrochloric acid, slows the heart rate, and lowers the blood pressure There is also dilatation of small blood vessels, some miosis is created, and there is interference with temperature regulation Recently the reserpine molecule has been altered to give a new derivative, syrosingopine (Singoserp), which has been reported to be more selective in that it has lost much of the tranquilizing action while retaining most of the hypotensive effect It is distinctly less potent, however, than reserpine, deserpidine and rescinnamine

It is important that the physician be familiar with the untoward effects exerted by the rauwolfia group of agents Unquestionably reserpine is capable of causing serious toxic effects In many reported cases it has not been the fault of the drug Frequently it is used unwisely, given in improper dosage, or administered without proper supervision

Dosage will be considered first In the medical use of reserpine it is usually not necessary to give more than 0 1 to 0 25 mg daily and there is generally very little to be gained in giving doses of more than 1 mg When the dose is over 0 5 mg daily, the danger of increased gastric secretion of hydrochloric acid, gastrointestinal ulcer, hemorrhage, or cramps with diarrhea is greatly increased Great care should be taken in giving this drug to patients having a history of gastro intestinal ulceration or overactive bowels Patients developing gastrointestinal distress should have the dose kept as low as possible and be put on a bland diet antacids, and antispasmodics If the distress is not promptly controlled reserpine should be discontinued

Likewise mental depression is far more common with the larger doses Reserpine should be avoided in patients with a history of or in frank mental depression and it should be stopped at the first sign of mental depression Larger doses pro duce parkinsonism and in some patients, interference with skilled movements may appear even on smaller doses This can lead to the clumsy use of hands stumbling and other evidences of impairment of skilled coordinated movement

Since reserpine increases appetite and patients frequently gain weight, this must be guarded against in those individuals where weight gain would be undesirable Some patients develop severe nasal obstruction, sinusitis and epistaxis The epistaxis may be severe and prolonged, and almost invariably requires packing of the nose for its control In rare instances it has caused fluid retention, congestive failure and gynecomastia in males and lactation in females. Finally, patients receiving reserpine should have the drug withdrawn for at least a week prior to gen eral anesthesia since serious collapse has been observed when patients receiving the drug are given a general anesthesia

active behavior in children They have been useful in obtaining weight reduct in tense, agitated compulsive eating, obese patients in whom their calming of er tional tension has permitted an effective dietary program to be carried out Th often afford relief in the menopausal syndrome, especially where there are anxie agitation and much emotional stress Patients with severe gastrointestinal d tress, gas nausea, vomiting bowel cramps and anorexia are frequently aided their tranquilizing action

Recently a great deal of interest has been focused on phenothiazines conta ing an alkyl thio substitution on the phenothiazine ring in the number 2 positio Thioridazine (Mellaril) is a methyl thio preparation of mepazine It is a usef although not highly potent, tranquilizer and does exert some antiemetic actio It is unique in that it does not produce extrapyramidal activity which is so com monly seen with prochloperazine and perphenazine This is a definite advanta in itself, but data obtained so far also indicate that it has much less toxicity th that seen in chlorpromazine The success of this compound has stimulated wo in this field and already several thio substituted phenothiazines are under stud

The success achieved in increasing potency by substituting a trifluorometh group in position 2 on the phenothiazine ring of chlorpromazine in place of th chlorine radical resulting in triflupromazine (Vesprin) will stimulate investigato to prepare other trifluoromethyl substituted preparations Trifluoro substitutio of the methyl group for chlorine in the number 2 position of the ring of prochlo perazine enhances the potency considerably as has been shown with trifluoperazin (Stelazine) Undoubtedly other preparations such as trifluoromethyl substitute thiopropazate (Dartal) and perphenazine (Trilafon) will soon be investigated It will also be most exciting when a trifluoromethyl thio substituted perazine an perphenazine are made available It could be that such preparations would no only greatly enhance activity but also would result in compounds much less toxi not only regarding blood and liver injury, but also free of extrapyramidal effect Certainly there is much yet to be done in the exciting field of phenothiazin synthesis and study

At the present time the potent prochlorperazine and perphenazine are gainin in popularity over chlorpromazine This is because they are even more potent that chlorpromazine and do not have its toxicity Trifluoperazine must be used care fully to get the desired effects but it has been proved to be effective when other have failed in severely psychotic patients For medical conditions most prefer to use prochlorperazine (Compazine), perphenazine (Trilafon) or thiopropazate (Dartal)

Meprobamate and Phenaglycodol—This group consists of meprobamate (Equanil Miltown) and phenaglycodol (Ultran), meprobamate being the most effective and most widely employed These agents are tranquilizers which were discovered in the search for a drug better than mephenesin They exert a de pressant effect on polysynaptic pathways similar to that observed for mephenesin Although meprobamate and to a much less extent phenaglycodol, exerts a calm ing, tranquilizing effect, these drugs differ from reserpine and the phenothiazines in that they do not block conditioned reflex activity in the rat potentiate strych nine or increase the threshold for electrical or chemical convulsive action Seda

activity, and an alarming reaction consisting of facial, jaw tongue, and neck muscle spasms has been observed after relatively small doses

The appetite is increased and obesity can readily develop Skin rashes are not uncommon and sensitivity to light occurs occasionally Some patients receiving chlorpromazine develop hypotensive episodes which at times are serious The more potent drugs of the series are much less prone to cause vascular collapse

The use of the phenothiazines in medicine is extensive They are excellent agents in suppressing agitation excitement and psychoneurotic anxiety, tension and fear The potent ones of the series are the most satisfactory tranquilizing agents available

Most of the phenothiazines exert an antiemetic effect Prochlorperazine and perphenazine exert a most potent antiemetic action and are used successfully in suppressing nausea and vomiting from uremia cancer radiation sickness and pregnancy after operations and from the use of narcotics and other drugs which cause local gastrointestinal irritation or activate the emetic chemoreceptor area A new phenothiazine thioperazine (Vontil) closely related chemically to prochlorperazine and perphenazine but differing from them by the addition of a dimethylsulfonate in the 2 position on the phenothiazine ring has in our hands proved to be the most effective of any antiemetic now available In a dose of 0 5 to 1 mg every 6 hours it exerts a highly effective antiemetic action without producing sedation or much tranquilizing action

Chlorpromazine promazine prochlorperazine and perphenazine have all been used successfully in facilitating drug withdrawal in patients addicted to alcohol barbiturates or narcotic drugs They markedly reduce the agitation discomfort emotional sensations and gastrointestinal disturbance These agents have been most useful in controlling the emotional stress agitation and gastrointestinal disturbances attendant on alcohol withdrawal in severe alcoholics In these patients the phenothiazines are far superior to reserpine since they suppress much of the nausea and vomiting which so frequently complicate chronic alcoholism

The central tranquilizing action of the potent phenothiazines exerts a beneficial effect on the itching agitation and distress accompanying severe dermatitis Frequently they are successful in bringing a neurodermatitis under complete control The most effective agent of the phenothiazines in controlling pruritus is trimeprazine (Temaril) This agent is a potent antipruritic which does not exert much tranquilizing action

The phenothiazines are useful in controlling hiccups and have shown remarkable action in relieving the distress of porphyria They occasionally are useful in controlling cardiac arrhythmia and are useful in calming the agitation and anxiety from pulmonary edema and severe asthmatic bronchitis

The weaker phenothiazines promazine and also chlorpromazine have been used to potentiate the effect of narcotic drugs and as adjuvants in inducing and maintaining a more smooth general anesthesia The antiemetic action is also helpful in controlling the nausea and vomiting so frequently seen with general anesthesia

There are many less common uses for the phenothiazines Chlorpromazine promazine and the more potent prochlorperazine have all been used successfully in relieving agitation in aged and senile patients as well as aberrant agitated over

Azacyclonol has been found useful in controlling psychotic states, particularly schizophrenic behavior Hallucinations and delirium have responded to it in some patients Abnormal psychologic behavior, delirium, hallucinations and disorientation, such as is seen in toxic infectious states and following drug therapy and fever are occasionally controlled by azacyclonol It does appear to be limited however in its value, since it frequently fails when a better effect might be expected Because of its erratic behavior it is difficult to assign this drug a definite role in therapy Some reports deny that it is of any value in disoriented states

Captodiamine, like the other agents of this series, is an antihistamine derivative It was developed from the diphenhydramine series Although it prolongs the action of pentobarbital, it does not produce much sedation and hypnosis does not result even following large doses It exerts a mild relaxing action on the gastrointestinal tract and has been found useful in treating tense, anxious patients with gastrointestinal symptoms such as occur with an irritable colon Many claims have been made for this drug, but as yet enough well controlled studies have not been carried out to support these claims

Benactyzine and hydroxyzine are still controversial drugs Some studies report them to be no better than placebos, while others find them highly useful Certainly there is a great deal of confusion as yet as to their real role in therapy In our hands neither has been proved satisfactory as a tranquilizing agent At least one controlled study on benactyzine has shown it to be no better than a placebo Benactyzine may have some use as an antiphobic acting drug in the treatment of fear and anxiety but further studies must be conducted before this use can be considered as established

Probably the best that can be claimed for benactyzine and hydroxyzine is that they are weak tranquilizers with erratic action which seem to exert a good effect in some patients and fail miserably in others The placebo effect unquestionably is highly significant in the use of these agents and the wise physician will stop them or substitute less expensive drugs such as phenobarbital or butabarbital in small doses from time to time to be certain that there is a real need

Sedatives —This group consists of sedatives used for their calming mild sedating effect Unquestionably mild sedation produces relaxation both mentally and physically Emotional tension is reduced and tense muscle states are relaxed by many sedative drugs For several decades phenobarbital has been a favorite for this purpose It has been a most useful agent in relaxing the tense anxious apprehensive individual Frequently it is the drug of choice in the limited stressful situation

Of all the barbiturates, phenobarbital exerts the most pronounced cortical depressant effect, and it may be this feature that has made it so popular It is however, a true sedative, and, if the dose is pushed, sedation and finally hypnosis result Tolerance develops fairly readily so that much of its action is lost in 2 or 3 weeks unless the dose is increased As with other barbiturates addiction can occur if the dose is sufficiently high usually 0 4 to 0 6 Gm daily, and is maintained for a period of 3 or 4 months Phenobarbital in the aged, senile and arteriosclerotic patient frequently causes confusion and disorientation and, as a consequence, does not calm but causes agitation and excitement Generally its use in

patient becomes drowsy and even ataxic However, even in large doses neither gives the sedation and hypnosis seen with the barbiturates Their action on interneuronal circuits, depressing multineuronal reflexes without significantly affecting reflex activity of monosynaptic transmission, probably enables them to reduce exaggerated reflex activity and thus reduce muscle tension, anxiety, and overreactivity to emotional tensions Meprobamate has been more thoroughly studied It is readily absorbed Blood levels are found in 30 minutes with peak levels at 2 hours It is widely distributed in the body, with the lungs, the kidney, and the liver having the highest levels Its major metabolite is the inactive hydroxymepro bamate It is metabolized by the liver, most of it being conjugated with glucuronic acid and approximately 20 per cent being slowly excreted unchanged in the urine

Meprobamate produces a dermatitis in approximately 2 per cent of patients Purpura and aplastic anemia have been observed Tolerance and then addiction develop when large doses of meprobamate are given This can be a serious problem in patients who have been given large doses for long periods of time, since definite withdrawal effects appear and these are often confused with the agitation excitement, and hyperactivity for which the drug was given in the beginning

Meprobamate and to a lesser extent phenaglycodol are useful agents in the treatment of the anxious tense, psychoneurotic patient who has no psychosis Some relief of muscle spasm and its attendant pain syndrome is afforded by these agents This relief, however, is not great and may be mainly a result of the seda tion and relief from anxiety and emotional tension rather than a specific action Phenaglycodol has recently been reported to be of some value as an anticonvulsant, but certainly it is not as potent as the usual anticonvulsant agents

Both meprobamate and phenaglycodol in spite of the widespread use of the former, are still somewhat controversial Many observers consider meprobamate not much better than a weak barbiturate like drug, and some consider both mepro bamate and phenaglycodol no better than placebos Undoubtedly neither is as useful or as effective as the more potent phenothiazines or reserpine These two agents are expensive and frequently do not accomplish much more than phenobarbital given in small doses which, of course, is of much less cost to the patient Since the placebo effect may be considerable in this type of medication, it is absolutely necessary for the physician to stop the use of these drugs at frequent intervals to determine if there is still any need for them or to try a less expensive agent and see if it will do as well

[Carisoprodol (Soma), a meprobamate congener (isopropyl meprobamate), has not been examined extensively enough to establish its value as a tranquilizer Ed]

Diphenylmethane Derivatives—This category consists of the derivatives of diphenylmethane azacyclonol (Frenquel), benactyzine (Phobex, Suavitil), captodiamine (Suvren), and hydroxyzine (Atarax, Vistaril) These agents are weak, somewhat erratic in behavior, and have not gained widespread use They resemble the antihistamines chemically and produce sedation They will potentiate barbiturate action block conditioned reflex activity, and can calm excited animal behavior They seem to raise the emotional threshold for external influences and reduce excessive reaction to stress There has been very little critical study of these compounds

much is known about its metabolism It has been reported to behave like a short acting barbiturate A central depressant action is exerted and is claimed to be useful in reducing irritable behavior and in calming anxiety tension states There is as yet insufficient data to assign this agent a definite role in therapy The early reports are promising, but limited experience with it on the part of the authors has not shown it to be in any way outstanding Much more must be known about its pharmacology and action in patients before a reasonable evaluation can be given

Phenyltoloxamine, an antihistamine derivative, is a most recently studied agent It produces sedative and moderate hypnotic effects with drowsiness and a slowing of psychomotor and mental performance resulting Relaxation follows the sedation and muscle tension is reduced It appears to have a cortical site of action *One study indicates it to be superior to phenobarbital* as a daytime seda tive There has been no autonomic disbalance observed from its use, and side effects have been minimal It may have value as a sedative type tranquilizer, but much more data must be accumulated before it can be recommended as a useful agent

SELECTED REFERENCES

Bein H J The Pharmacology of Rauwolfia Pharmacol Rev 8 435, 1956

Berger, F M, Campbell, G L, Hendley, C D, Ludwig B J, and Lynes T E The Action of Tranquilizers on Brain Potentials and Serotonin, Ann New York Acad Sc 66 686 1957

Council on Pharmacy and Chemistry Blood Dyscrasias Associated With Chlorpromazine Therapy, J A M A 160 287, 1956

Cummins, J F, and Friend, D G Use of Chlorpromazine in Chronic Alcoholics Am J M Sc 227 561, 1954

DiMascio, A Klerman, G L Rinkel, M, Greenblatt, M, and Brown J Psychophysio logic E [illegible] otropic Agent A Comparative Study [illegible] 115 301, 1958

Friedgood, C E [illegible] horazine) in the Treatment of Intract [illegible]

Friend D [illegible] 1953, 1958

Friend, E [illegible] iew Chlorphenothiazine [illegible] 732, 1957

Hochman [illegible] England J Med 259 583 1958

Hollister L E Complications From the Use of Tranquilizing Drugs New England J Med 257 170, 1957

Kinross Wright, J *Newer Phenothiazine Drugs in Treatment of Nervous Disorders* J A M A 170 1283, 1959

Korst D R Agranulocytosis Caused by Phenothiazine Derivatives J A M A 170 2076 1959

Lear, E, Pallin I M Chiron A E, Rousseau L and Aochi O Comparative Studies of Tranquilizers Used in Anesthesia, J A M A 166 1438, 1958

Mechanic R G and Meyers L Chlorpromazine type Cholangitis New England J Med 259 778 1958

Melby J C, Street J P and Watson C J Chlorpromazine in Treatment of Porphyria J A M A 162 174 1956

Meyer, L M, Heeve, W L, and Bertscher, R W Aplastic Anemia After Meprobamate New England J Med 256 1232, 1957

Mohr R C and Mead B T Meprobamate Addiction New England J Med 259 865 1958

O Hara [illegible] ing Prochlorperazine, New Eng [illegible]

Perera, C [illegible] he Administration of Rauwolfia [illegible] 59

Werner, ([illegible] Ulcer During the Administra

West, W [illegible] Ann Int Med 48 1033 1958

the aged should be avoided Its cortical depressant action usually produces an unfavorable action in patients with Parkinson s disease, the tremor and agitation increase and if the dose is sufficient or if the patient is very susceptible to its action, it may seriously incapacitate the individual An occasional patient develops a generalized skin rash and rarely a macrocytic anemia appears after long continued administration

On the whole, however, phenobarbital is exceedingly well tolerated, and, except for its tendency to create too much sedation in many patients it is a highly satisfactory drug in the treatment of the agitated, anxious overactive patient who cannot sleep and is being subjected to a temporary emotional strain It is by far cheaper than any of the other nonsedative agents and is often more effective

Butabarbital (Butisol) in doses comparable to phenobarbital has also been used with success in treating the agitated, tense individual It is thought by some to be less prone than phenobarbital to produce undesired sedation in the doses employed It, like phenobarbital is cheap and frequently affords the right degree of relaxation It is an excellent alternate for phenobarbital and some feel it is even a better drug

Mephobarbital (Mebaral) has also been recommended for its mild calming action with a minimum of sedation Experience with it as a sedative tranquilizer is not sufficient as yet to ascertain its true status It is doubtful however, if it will be used extensively since it lacks the unique properties found useful in the more potent agents

Other sedatives which have been recommended as sedative type tranquilizers are glutethimide (Doriden), methyprylon (Noludar), and ethchlorvynol (Placidyl) Unquestionably these sedatives in small doses are useful in quieting the agitated tense patient They are all central nervous system depressants and effective sedatives Their use as tranquilizers is not extensive, and certainly more experience with them is needed before they can be assigned a definite role Glutethimide produces a skin rash in a fair number of patients and addiction to it has been reported Methyprylon and ethchlorvynol are capable of causing anorexia nausea, mental confusion ataxia and hangover

Miscellaneous Agents —This category consists of ectylurea (Nostyn), oxanamide (Quiactin) and phenyltoloxamine (Histionex) These agents have only recently been introduced as tranquilizers and as yet have gained no widespread recognition or use Ectylurea exerts a mild sedating effect and has been reported as useful in mild anxiety and tension Because of its low toxicity and mild action it has been used with success in diminishing restlessness irritability, and tension in children It is of little or no value in the seriously agitated overactive, excited tense patient Ectylurea has a low degree of toxicity Large doses are tolerated well with only a sedative hypnotic effect resulting It is rapidly absorbed and metabolized with nearly two-thirds of the ingested dose appearing as urea in the urine within twelve hours One case of cholangiolitic hepatitis with jaundice from ectylurea in a dose of 300 mg 3 times a day has been reported Its role as a tranquilizer is not well established and as yet its use is not extensive

Oxanamide a new agent is as yet a comparatively little used tranquilizer Chemically it differs considerably from any of the other agents and as yet not

against a great deal of anxiety during psychotherapeutic procedures The patients maintained better emotional equilibrium, and the psychotherapy could be concentrated on their problems Often very anxious patients need a great deal of reassurance or other ego supportive measures, and much of the psychotherapy has to be devoted to this particular task In patients who were under drugs this function was performed by the medication, particularly so in patients who were psychotic or suffering from a neurotic disturbance which produced a great deal of anxiety and tension

Clinical Applications

Manic-Depressive Psychoses —Thorazine is very effective in controlling manic states, elation, and overactivity Some prefer giving Thorazine by injection to a patient in an acute manic excitement, others give it orally By injection it is possible to cut through excitement quickly, with oral treatment it takes somewhat longer Thorazine is equally effective in acute and chronic states, both respond favorably The psychomotor excitement in these patients is the most outstanding symptom influenced by Thorazine

However, the same cannot be said about the manic depressive depressed patient Depressions in general, with the exception of some of the agitated depressions, do not respond well to Thorazine In some cases it is not only ineffectual but it can also aggravate the existing depression This is especially true in patients suffering from a 'retarded" depression It is less effective in tense or agitated depressions Sometimes the tension or agitation present in these patients is not clearly recognized In doubtful cases these patients should be treated under close supervision

In manic depressive states, rauwolfia is not used extensively This is due to the fact that rauwolfia acts more slowly than Thorazine and, therefore, is not used to a very large extent to influence conditions considered to be acute Rauwolfia is ineffective in patients suffering from depression Furthermore, there is a considerable danger that rauwolfia may aggravate the existing depression and as will be pointed out later, sometimes may precipitate depressions

In manic states different compounds such as Thorazine, Compazine, Sparine, etc , can be used In patients who are quite excited Compazine can be given in dosages of 10 to 20 mg (2 to 4 ml intramuscularly) The injection should be given deeply into the upper outer quadrant of the buttock In acutely disturbed patients the initial dosage may be received every 2 to 4 hours If Sparine is used, it can be given intravenously in dosages of 100 to 200 mg When the patient has calmed down maintenance dosage can then be instituted by the oral route Thorazine also can be used in manic patients and can be given intramuscularly or orally The initial dosage with Thorazine should be 50 mg, 3 times daily, and then brought up fairly rapidly to a level which controls the manic excitement effectively In some patients several hundred milligrams will have to be used to control the excitement I find it best to build up dosages in these patients rather rapidly increasing it day by day until the manic state is controlled not waiting several days before maximum dosage is reached After the manic state is controlled, I maintain the patient on that dosage for about 2 weeks and then gradually with

Chapter 15

THE CHOICE OF SEDATIVES AND TRANQUILIZERS FOR PSYCHIATRIC DISORDERS

Paul H. Hoch, M.D.

TRANQUILIZERS

In the discussion which follows, chlorpromazine (Thorazine) and the rauwolfia preparations, the best known and most tested of the so-called tranquilizing agents, will be considered in the main While there are quite a number of other compounds in use not enough experience with them has been collated and only in the case of those which have been tested extensively is there sufficient knowledge to be able to formulate substantial conclusions Opinion about the extent of their efficacy remains controversial, even in the case of Thorazine and the rauwolfia compounds, although they have been used extensively in practically every form of mental and emotional disorder in the last few years

It is important to emphasize that these drugs do not cure definite mental disorders such as schizophrenia or manic depressive psychosis, they influence symptoms to a varying degree Their effectiveness cuts through diagnostic lines in excitement or manic excitment states in the framework of manic-depressive psychosis, schizophrenia, and cerebral arteriosclerosis These are all influenced equally well The same is true about tension and anxiety states in the different neurotic groupings

Relationship of the Tranquilizing Drugs to Psychotherapy

The relationship of the tranquilizing drugs to psychotherapy is a very important and intricate subject still under investigation Some patients find that because the drug completely controls their anxieties and tensions they do not need psychotherapy How many patients have the ability to work out their conflicts if under the drug alone has not been established Many of the patients who feel very much better under the influence of the drug still require psychotherapy in addition to the medication because they have problems and conflicts which are not solved by taking the drug alone In my experience psychotherapy with patients who responded well to the tranquilizing drugs was much more comfortable and profitable than with those who did not receive the drug These patients were cushioned

Depending on symptoms, in some cases hospitalization is to be preferred and in others it may be omitted Depressed, suicidal schizophrenic patients or acting out aggressive patients are treated by preference, in a hospital It is most important that psychotic patients treated on the outside with tranquilizing drugs be carefully supervised With proper supervision a considerable number of acute schizophrenic patients can be treated in family settings, clinic settings, or in a day hospital setting If appropriate supervision cannot be provided or if the patient does not accept it, hospitalization is essential if these drugs are to be used safely

It also can be stated that if a patient is admitted to a hospital he can be treated more rapidly and effectively today than formerly The hospital phase of the treatment is shorter than by older methods and, after improvement has been observed he can be transferred to an ambulatory status I feel that, at present the greatest gain made in the treatment of schizophrenia with the tranquilizing drugs is the shortening of the treatment time It is most important also that the shorter stay of the patient in the hospital prevents the schizophrenic patient from deteriorating and permits his reintegration into the community faster and better than in the case of those who formerly spent a longer time in the hospital

Chronic Schizophrenia —Second, the tranquilizing drugs are widely used in chronic schizophrenic patients A large number of chronic patients were treated in the different state hospitals to determine what could be accomplished with tranquilizers In the beginning there was a great deal of enthusiasm some believing that the great majority of hospitalized chronic schizophrenic patients would respond and that they could be discharged This is not quite the case Many chronic schizophrenic patients show a change in their behavior and can be considered improved However, even though their management in the hospital is far simpler, many of them do not improve to such an extent that they can leave the hospital To a large extent this also depends on the kind of environment to which they return If the environment is supportive they are in a far more favorable position than if the environment is nonsupportive or if they have to be released into a strange environment Many chronic schizophrenic patients, even though they show improvement with the tranquilizing drugs, need an understanding environment or they are not able to function

How many chronic schizophrenics can be released from the hospital is still not known Statistics vary depending upon the severity of the type of schizophrenia treated and on the supervision which can be provided after release I feel that about 15 per cent of the chronic patients can be released provided the community environment is such that they receive some support for their functioning Many of these patients have to be kept for long periods—sometimes indefinitely—on tranquilizing drugs This maintenance treatment is an important part of the therapy in the treatment of a chronic schizophrenic patient

Third, tranquilizing drugs are used in chronic schizophrenic patients who do not improve to such an extent that they can be released from the hospital Some aggressive, destructive, and deteriorated patients benefit from the drug through alteration of their behavior patterns permitting better functioning especially in relation to others, even though many of them do not improve to such an extent that they can be released The basic rule applies here in the same way in which it does in shock therapy The duration of the sickness is an important

draw the drug continuing however with the minimum effective maintenance dose If on withdrawing the drug the patient s symptoms return the dose of the drug is elevated until the symptoms are controlled

The question arises whether a patient suffering from manic depressive psycho sis, manic type, should receive maintenance treatment between attacks Most psychiatrists today maintain the patient on the drug for a while after the manic attack has subsided and later withdraw the drug We do not know whether, in patients who have the tendency toward repeated manic attacks, continuous admin istration of the tranquilizing drugs will prevent the recurrence of attacks for con clusive investigations have not been made on this issue

Many use Thorazine in conjunction with electroshock treatment to break through the manic excitement It has been claimed by some that in conjunction with electroshock treatment Thorazine reduces the number and intensity of the use of Thorazine in combination with electroshock therapy is not without danger, shock treatments required On the other hand there are some who feel that the and therefore the use of this combination should be weighed carefully

Involutional Psychoses—In the involutional psychoses which show either a depressed picture or a paranoid one Thorazine can be used if the patient shows ten sion and agitation in connection with the depression Agitated tense depressions are quite common in the involutional age group and they respond to Thorazine even though it may take somewhat longer to influence the psychosis than with electroshock therapy In some patients, however, Thorazine controls only the psychomotor excitement and agitation and does not influence the depression These patients must have electroshock treatment again The paranoid form of involu tional psychosis responds to Thorazine quite well provided the treatment is ap plied for a sufficient length of time

Schizophrenia—The use of the tranquilizing drugs for treatment is especially important in cases of schizophrenia This disorder constitutes the bulk of the mental hospital population and can be considered the largest and one of the most important psychiatric diagnostic entities The tranquilizing drugs are used in three ways in schizophrenic disorders

Acute Schizophrenia—First these drugs are used in the treatment of acute schizophrenics if they are not too disturbed to remain in the community setting It is hoped that in these patients the use of the tranquilizers can provide enough symptomatic relief to eliminate the need for hospitalization We have no reliable statistics on the extent to which these drugs are able to accomplish this purpose clinical opinions are contradictory Some feel that the use of the tranquilizing drugs does not prevent the ultimate hospitalization of these patients On the other hand there are those who feel that a considerable number of schizophrenics can be treated in a clinic setting if they receive these drugs under proper supervision

At present generalizations are not permissible In each evaluation of symp tomatology social setting and other factors will determine how far a schizophrenic patient can be carried with the help of tranquilizing drugs on an ambulatory basis and when hospitalization is necessary Tranquilizing drugs do not influence mas sive schizophrenic symptomatology immediately, unless they are given by injection or orally in such large doses that side effects may appear Such therapy can be safely conducted only in a hospital

phrenic patients respond better to one type of tranquilizing drug than to another, and, therefore, some experimentation with the various drugs is warranted

In my experience very few of these patients improved to such an extent that the tranquilizing drugs could be completely withdrawn The majority have to take the drug for an indefinite period Until a point of stabilization is achieved, these patients also need psychotherapy They are especially prone to get into difficulties if they are not followed closely and given enough psychotherapeutic help for their problems As yet we do not have reliable statistics indicating how many pseudo neurotics respond well to these drugs There are some who do not benefit from them On the other hand, I have seen some who for the first time are able to function in relative comfort without being constantly ridden by anxiety and other neurotic manifestations

Psychoneuroses —The use of the tranquilizing drugs in the psychoneuroses is far less well established than in the psychoses, although today a very large number of neurotic patients are prescribed these drugs by their physicians Therefore, it is very important to assess their value in such patients

It has to be emphasized that evaluation in this group of patients is far less reliable than in the psychotic individuals, for there are many pitfalls in evaluating therapeutic results in neurotic patients In addition these drugs were first used and studied in mental hospitals so that the basic information on their efficacy and dangers applies to the psychoses specifically and, without the support of careful investigation should not be taken to apply to the neuroses The neurotic functioning of a mildly disturbed person can be influenced in so many ways that only the most carefully conducted investigation can provide reliable information on causal connections It is also customary to give some form of psychotherapy to these patients even if it is no more than reassurance It is then difficult to separate the response to the drug from the response to psychotherapy It also has to be emphasized that many neurotic patients respond to a given drug just as long as publicity and mass suggestion convince them that they are being treated with a very potent new therapeutic agent When the suggestive influence wanes the therapeutic efficacy of the drug wanes with it

The tranquilizing drugs are used in all kinds of neurotic disorders In our experience it is difficult to foretell how a patient will respond We have patients with very similar symptoms who give dissimilar responses In some the symptoms are reduced or even eliminated, in others the symptoms are not influenced and sometimes even aggravated, and in still others even new symptoms appear A general statement, therefore, that any or even many neurotic patients will benefit from the use of these drugs is unwarranted

The discussions in the literature on the efficacy of these drugs in neurotic individuals are somewhat contradictory Some believe that if patients are given the drug for a few weeks or months the neurotic manifestations disappear This has not been my experience It is true there are some patients who after being treated for a few months do not need any further treatment and function well However, other patients have to take the drug for a prolonged period or a relapse will occur There is no reliable information about the outcome of many of the neurotic disorders in patients who have been taking the tranquilizing drugs for several years

factor Chronic schizophrenics of 10 years duration have less chance of recovering and functioning normally than schizophrenics who have been sick for only one year, but it has to be emphasized that there are exceptions, especially in some types of schizophrenia in which deteriorative processes do not occur commonly or occur only relatively late in its course

The great value of the tranquilizing drugs rests not alone on their efficacy in individual patients but also on the fact that it is possible to transform the atmosphere of the disturbed services into one which is much the same as that of the wards where quiet cooperative patients are housed Where formerly many patients on the disturbed wards were isolated in special rooms, this is much less frequently necessary Prior to the use of these drugs the disturbed wards were bare of furnishings curtains table clothes and eating utensils Today the patients on these wards are quiet composed and engaged in various activities The furnishings and organization scarcely differ from those of wards formerly used for quiet well behaved patients

Effects of Tranquilizers in Schizophrenic Patients —The tranquilizing drugs directly affect the mental symptomatology of schizophrenic patients It has not been worked out in detail but in general the emotional symptoms respond best to the tranquilizing drugs Anxiety aggression overactive behavior, delusions and hallucinations are symptoms which can be controlled quite effectively by the tranquilizers The drugs have less influence on intellectual disorganization and on schizophrenic thinking

The different subgroups in schizophrenia have somewhat different reactions to the tranquilizing drugs The paranoid and catatonic forms of schizophrenia respond best The hebephrenic and simple forms of schizophrenia often show improvement but in many chronic cases the improvement does not go so far as to allow the patient to adjust to the community These, however are general observations and there are many exceptions to the rule The best policy is to treat the patient for a period of time to see what can be accomplished rather than to reject the patient for treatment because of clinical preconceptions

The basic rule of practically all treatment in schizophrenia also applies to treatment with tranquilizing drugs It is more complicated to treat and to achieve results with chronic patients than with acute patients Disorganization of thought and behavior if detached from emotional components, are less influenced

The response to tranquilizers of schizophrenics with mixed symptomatology who show manic depressive features is sometimes difficult to judge The manic or excited phase is usually well controlled A depression in a schizophrenic is sometimes controlled, but at other times the depressive effect is not influenced as much by the tranquilizing drug as are other symptoms In the pseudoneurotic form of schizophrenia the tranquilizing drugs are important, because in many of them the constant state of anxiety shown by these patients is controlled In turn, many of the neurotic manifestations are controlled

There are pseudoneurotic schizophrenics however, who either do not respond to the tranquilizing drugs or even become worse They therefore, have to be carefully supervised in the first phase of their treatment There are also patients who often complain about side effects which may or may not be present, but preoccupy the patient's attention It has to be emphasized that some pseudoneurotic schizo-

blood pressure, sleep, appetite, and thermal regulation, showing influence on vegetative regulative centers Studies in animals *pointing to a special influence of these* drugs on the midbrain and brain stem are supported by the clinical observation that the tranquilizing drugs do not interfere to any great extent with cortical function intelligence memory, and orientation Clinical investigations indicate that the tranquilizing drugs are also selective sedatives especially affecting anxiety and tension

Toxic States —The tranquilizing drugs are also used in toxic states in which the patient is delirious Delirium due to alcohol drugs, or infection often responds rapidly to Thorazine The confusion and the hallucinatory manifestations subside rather quickly under the influence of the drug Thorazine can be used in all acute confusional states to advantage, especially if the patient shows hyperactivity and agitation Here the tranquilizing drugs are superior to the usual sedatives, because consciousness is not influenced and the drugs themselves do not produce secondary manifestations so common after barbiturates in this type of patient

The tranquilizing drugs Thorazine and rauwolfia, also have side effects which have to be taken into consideration, because they can complicate treatment and make it necessary to withdraw the drug or to apply special therapeutic measures Fortunately the side effects are usually not very serious Nevertheless, it is very *important to pay attention to them The side effects of these drugs can be divided* into two kinds, physical and psychic

CHLORPROMAZINE —One of the most important side effects of Thorazine is jaundice This has been reported by different authors in from 1 to 5 per cent of their cases Jaundice may occur in any type of patient regardless of dosage It is occasionally seen after a week or two of Thorazine, but it is more common in patients who have received the drug for months Some patients develop jaundice slowly, in other patients the jaundice comes on rather suddenly in connection with fever and grippelike symptoms

If the patient should develop abdominal symptoms the possibility of side effects due to Thorazine should be excluded because the clinical picture sometimes simulates that of an extrahepatic obstruction

Toxicity studies with Thorazine on animals have not shown any impairment of the liver parenchyma Similar observations were made on *human beings* The pathologic examination of biopsy specimens showed a stasis of bile in the intra*lobular canaliculi with lymphocytic infiltration* Today jaundice is considered to be caused by the lymphocytic infiltration *Occasionally eosinophils are also present*

Liver function tests in a series of patients who had been given Thorazine were usually within normal limits It has to be noted that many tests for bile in the urine *may react chemically* with Thorazine, giving false positive results If the patient develops jaundice, Thorazine should be withdrawn The jaundice usually subsides in about 2 weeks but there are cases where the jaundice lasted much longer In a number of patients the dose can be reduced and the drug given again without causing a recurrence of jaundice In others, however each time *Thorazine is given* jaundice develops

Special treatment for jaundice is not often necessary Some treat the patient with a high protein high calorie diet, some give the patient ACTH or cortisone,

Many advocate the use of chlorpromazine in a number of psychosomatic conditions An intensive study of these disorders still has to be made, although Delay and Deniker have found chlorpromazine very useful and Winkelman is of the same opinion

Senile and Arteriosclerotic States *—Tranquilizing drugs are also used in senile* and arteriosclerotic states in which they have had beneficial effects on agitation anxiety reactions, delusions hallucinations and disorderly behavior Many of these patients who are belligerent defensive and difficult to handle become cooperative and tractable It is important to emphasize that these drugs sedate the patient without producing a clouding of mental processes so often observed with sedatives Actually some confused and memory impaired patients in this group function better Most likely this is because some emotional interference is removed It must be stated that the tranquilizing drugs have no influence on true dementia and thus intellectual deterioration is not influenced by these compounds

The Mode of Action of the Tranquilizing Drugs

The mode of action of the tranquilizing drugs is not clear Many observations have been made in the last few years on their action but no one knows precisely how they influence emotional symptomatology Actually it is very difficult to classify these drugs because they do more than sedate For instance, chlorpromazine *is quite effective in relieving acute confusional states in the organic psychoses* Confusion is not explained clinically by overactivity alone other functions are involved Sedatives like barbiturates and bromides have no influence on a confusional state Therefore the tranquilizing drugs in addition to sedating must have other influences on the central nervous system If we study the action of the tranquilizing drugs they do not seem to sedate every psychic function uniformly Some functions are reduced in intensity and other functions are even intensified The drugs influence certain symptoms of the psychosis especially those which are due to overreaction That the tranquilizing drugs also suppress symptoms but do not affect the basic structure of the psychosis is brought out by the fact that the majority of patients have to take the drug for a long period of time even indefinitely to be free of their symptoms

A number of hypotheses have been put forward to explain the site of action of the tranquilizing drugs At present all the available experimental and clinical observations do not permit a definitive opinion on where they produce their pharmacologic effects Neurophysiologic observations in animals implicate the mid brain and the reticular substance but details of mode of action are still controversial The biochemical investigations are especially concerned with the relationship of the tranquilizing drugs to adrenergic mechanisms and more lately serotonin mechanisms in the central nervous system None of these studies have satisfactorily explained their efficacy

The clinical observations with the tranquilizing drugs indicate that the mid brain is implicated This does not exclude action on other parts of the central nervous system Large doses of chlorpromazine or reserpine often produce parkinsonism a clear indication of the involvement of the subcortical gray matter In addition the tranquilizing drugs in varying degree affect vegetative regulation

ness Some patients complain of being depressed and not being able to function, others that they feel they are being driven, that they are *restless, and that they* are not able to keep still Occasionally, instead of relieving them, Thorazine reinforces the existing psychic symptoms In general, these complications are not serious, and when the amount of the given drug is reduced or the drug is withdrawn, the symptoms disappear Some anxious patients are upset by the experience *These complications can be handled much* more easily when the patient is seen periodically and receives some psychotherapy in addition to the drug than when the patient receives the drug alone

Rauwolfia —Rauwolfia preparations, especially reserpine, which has been studied extensively, are also followed by complications Nasal stuffiness, tremulousness, and mild gastrointestinal disturbances are quite common Some patients complain about fatigue, drowsiness, and increased salivation, some develop edema *of the face or the feet These complaints usually disappear after the treatment* continues for 2 or 3 weeks In some patients convulsions have been seen, usually only 1 or 2 seizures About 5 per cent of the patients who receive large doses of rauwolfia develop typical parkinsonism which usually disappears on reduction of dosage Nevertheless, a number of therapists continue giving the medication, when they feel the patient's mental condition warrants it, even though the patient develops parkinsonism This requires expert judgment, usually discontinuance of *the drug is preferable*

In some patients overdosage of reserpine may cause a typical toxic psychosis characterized by loss of appetite, confusion and other manifestations of organic psychoses This disappears when the drug is reduced One of the most common complications with rauwolfia preparations is the precipitation of depression This occurs most commonly *in hypertensive individuals of middle age We observed* such depressions by reserpine not only in patients receiving larger doses but also in those who received comparatively small doses over a prolonged period Occasionally Thorazine also is able to precipitate a depression or aggravate an already existing one In most instances the depression disappears when the drug is withdrawn In some patients the depression remains so profound that *electroshock* has to be used to eliminate it

Attention should be drawn to the important fact that in those patients who are depressed the tranquilizing drugs *do not prevent suicidal* behavior Therefore, if depressive features are present in the clinical picture, this should be taken into special consideration

Meprobamate

Meprobamate (Miltown, Equanil) is related to mephenesin, which has been widely used in a variety of conditions in which muscle spasm is a factor Miltown has been advocated and used for anxiety and tension states, including insomnia and various psychosomatic conditions for muscle spasm in rheumatic and related disorders and for epilepsy (petit mal)

My experience with this compound is that it is ineffective in patients suffer*ing from an acute organic psychosis* and for patients suffering from an acute schizophrenic break who have massive symptoms such as delusions and hallucinations Generally speaking, the other tranquilizing drugs such as chlorpromazine

which is felt to shorten the duration of the jaundice I withdraw the drug and allow the patient to recover spontaneously and give special medication only if the jaundice is prolonged

Much more serious than the jaundice is the influence of Thorazine on the hematopoietic apparatus Leukopenia is fairly common in patients who receive Thorazine, at times agranulocytosis develops this has led to several deaths In patients who complain of sore throat or other signs of infection agranulocytosis should be considered If the blood count indicates its presence the drug should be immediately discontinued and antibiotic treatment instituted While the presence of a mild leukopenia is not an indication for discontinuance of the drug, serious leukopenia demands it

Another complication of Thorazine is postural hypotension This occurs more often after the injection of Thorazine than after oral administration Patients who try to lie down or get up suddenly experience dizziness or faintness These patients should be carefully observed The hypotensive effect of Thorazine may sometimes be counteracted with norepinephrine but epinephrine should not be used because Thorazine may reverse its action For some patients it is sufficient to remain in a recumbent position for about a half hour after which the symptoms usually disappear If the hypotensive effect of the drug is prolonged or very intense it may progress into a shocklike condition these patients should be put to bed and procedures to elevate blood pressure applied

In patients suffering from conditions in which a fall in blood pressure may have serious consequences Thorazine should be used with caution it should not be injected because the action of the drug develops more quickly and with more intensity than when given orally

Thorazine also produces dermatologic reactions These are fairly common but usually mild The patient may complain of an urticarial rash which disappears when the drug is withdrawn Sometimes it disappears even though the drug is continued Thorazine induces photosensitivity and patients using it should be advised not to expose themselves to intense sunlight If large doses of Thorazine are given for a long period some patients develop a typical parkinsonian syndrome This disappears when the drug is withdrawn

Engorgement of the breast with lactation has been reported in patients who received large doses of Thorazine This condition disappeared when the drug was withdrawn

Thorazine prolongs and intensifies the action of many central nervous system depressants such as barbiturates alcohol and narcotics This fact should be taken into consideration if the patient receives barbiturates or narcotics in combination with Thorazine or if he takes alcohol In our experience this potentiation is not marked when small doses are used but it increases with larger doses To prevent accidents patients who receive tranquilizing drugs should be told that they should not take other medication or alcohol without the physician s knowledge

I would like to call attention to the fact that Thorazine can also produce psychic complications These are more common in nonpsychotic patients than in psychotic ones and they usually occur in the initial phase of the treatment Some patients complain about feelings of depersonalization or that they feel strange peculiar, and out of contact At times they complain of marked lethargy and weak

should receive the amount of medication which adequately controls his symptoms It is obvious that the use of low dosage has certain advantages, especially in an ambulatory setting It should be stated, however, that in some patients who do not respond to small doses, gratifying results will be obtained when larger doses of the same drug are used, even though this necessitates hospitalization for a time

With psychotic patients I usually begin with 25 mg of chlorpromazine, 3 times a day If the patient is disturbed, larger doses are given Dosage is then increased either daily or every 2 or 3 days until symptoms are controlled Some need 1,000 or 1 500 mg of chlorpromazine daily and some even larger doses—up to 4 000 mg It is not clear how far one can or should go and where the point of no return lies I feel that if a patient does not respond to 1,200 to 1,500 mg of chlorpromazine over a reasonable period, much larger doses will not accomplish a great deal There are exceptions to this stand, but again I would like to stress that dosage is a highly individualized matter and the good therapist will experiment with dosage The same applies to rauwolfia

Duration of Treatment—How long the treatment should continue must also be individualized I feel that a patient should be treated for at least 4 months with adequate dosage before it is decided that he is not responsive to a drug Then it is advisable to change to another tranquilizer Some patients, for a reason not yet known, respond to one tranquilizing drug and not to another, but there are patients who are refractory to all the tranquilizing drugs which are in use today

After having treated the patient for 3 to 4 months, it is my custom to reduce dosage to a maintenance level In some patients the adjustment of maintenance dosage involves quite a bit of experimentation

Some patients show an adaptation to the drug, complaining that some symptoms are returning This is an indication to raise dosage until the patient is again symptom free I have observed a large number of patients in whom adaptation developed, they functioned quite well, however, after dosage was elevated But the reverse can also occur and, in some patients needing a fair amount of the drug dosage can be successfully cut down to a comparatively small amount In some patients the drug can be discontinued after a few months In many patients, however, the tranquilizing drugs have to be given for a long time and, in some, indefinitely Periodic attempts should be made to reduce or eliminate the use of the drugs, otherwise the patient will continue to take the drug even when it is not needed

True addiction to the tranquilizing drugs seemingly does not develop in the same sense as addiction to morphine Habituation, however, may occur

SEDATIVES

This section also deals with sedation applying to psychiatric conditions Most of the sedatives which were formerly used were hypnotics applied in smaller dosages than those which induce sleep After the introduction of tranquilizing drugs, the use of these diminished considerably

Bromide—Bromide was one of the most common sedatives of the last century It depresses central nervous system function, and in dosages necessary for sedation it has a cortical action In smaller doses, bromide causes mental calmness, in

and the rauwolfia preparations are far more effective than meprobamate in psychotic patients, and even psychotic patients with mild symptoms have reported that they feel more relaxed after these than after meprobamate

Meprobamate is used more effectively in neurotic than in psychotic patients The reaction of neurotic patients to this drug is unpredictable, however There are some patients who feel more relaxed and show less anxiety, while other patients with very similar symptomatology do not We have no clue, physiologic or psychologic, why one patient responds to meprobamate whereas another with the same symptoms does not

There are side effects from meprobamate Drowsiness is reported with some frequency Some patients develop an allergic reaction in the form of urticaria or an erythematous rash which is either localized or general In some severe reactions there was a hemorrhagic type of rash, fainting spells, and bronchial spasms In such patients the use of the drug should be discontinued and antihistamines and cortical steroids given

Choice of a Tranquilizer

The selection of the tranquilizer for the treatment of different psychiatric conditions is not based on clear cut indications, but mainly on the preference of the clinician In a psychotic patient with an acute condition such as excitement, manic attack, or where a considerable amount of psychomotor activity is present, chlorpromazine is preferable to rauwolfia because of its quicker action

Some patients respond better to one drug than to another, but there are no definite clinical guides, at the present time on how to determine this in advance of trial I feel that generally chlorpromazine is more effective orally than reserpine Patients taking reserpine usually need injections for a while before they can be switched to oral administration On the other hand, it must be taken into consideration that chlorpromazine has more frequent complications than rauwolfia In the patient who has liver involvement rauwolfia is preferable to chlorpromazine

I feel that chlorpromazine is the drug which is most effective and has the widest range of applicability the rauwolfia preparations are second Azacyclonal (Frenquel), meprobamate (Miltown, Equanil), and pipradrol (Meratran) are far less effective in psychotic patients There have not been enough observations in different hospitals and clinics with prochlorperazine (Compazine) and promazine (Sparine) and the other newer phenothiazine preparations to have fully assessed them in relation to Thorazine My tentative opinion is that they are not as effective as Thorazine in prolonged treatment of psychotic patients but that they have a definite place in the therapeutic armamentarium for the milder emotional disorders and psychoses

Regimen for Use of Tranquilizers

Dosage —The dosage of the tranquilizing drugs is a highly individual affair For instance, some patients regardless of their diagnosis and symptomatology, will respond to 50 mg of chlorpromazine daily while others with similar symptomatology will need 1 500 mg Some patients respond to 1 mg of reserpine while others need 18 to 20 mg Dosage must be tailored to the patient's condition In addition some clinicians prefer low dosage and others high dosage I feel the patient

should receive the amount of medication which adequately controls his symptoms It is obvious that the use of low dosage has certain advantages, especially in an ambulatory setting It should be stated, however, that in some patients who do not respond to small doses, gratifying results will be obtained when larger doses of the same drug are used, even though this necessitates hospitalization for a time

With psychotic patients I usually begin with 25 mg of *chlorpromazine*, 3 times a day If the patient is disturbed, larger doses are given Dosage is then *increased either daily or every 2 or 3 days until symptoms are controlled* Some need 1,000 or 1 500 mg of chlorpromazine daily and some even larger doses—up to 4 000 mg It is not clear how far one can or should go and where the point of no return lies I feel that if a patient does not respond to 1,200 to 1,500 mg of chlorpromazine over a reasonable period much larger doses will not accomplish a great deal There are exceptions to this stand, but again I would like to stress that dosage is a highly individualized matter and the good therapist will experiment with dosage The same applies to rauwolfia

Duration of Treatment—How long the treatment should continue must also be individualized I feel that a patient should be treated for at least 4 months with adequate dosage before it is decided that he is not responsive to a drug Then it is advisable to change to another tranquilizer Some patients for a reason not yet known, respond to one tranquilizing drug and not to another, but there are patients who are refractory to all the tranquilizing drugs which are in use today

After having treated the patient for 3 to 4 months, it is my custom to reduce dosage to a maintenance *level In some patients the adjustment of maintenance* dosage involves quite a bit of experimentation

Some patients show an adaptation to the drug, complaining that some symptoms are returning This is an indication to raise dosage until the patient is again symptom free *I have observed a large number of patients in whom adaptation* developed they functioned quite well, however, after dosage was elevated But the reverse can also occur and, in some patients needing a fair amount of the drug dosage can be successfully cut down to a comparatively small amount In some patients the drug can be discontinued after a few months In many patients however, the tranquilizing drugs have to be given for a long time and, in some, indefinitely Periodic attempts should be made to reduce or eliminate the use of the drugs, otherwise the patient will continue to take the drug even when it is not needed

True addiction to the tranquilizing drugs seemingly does not develop in the same sense as addiction to morphine Habituation, however, may occur

SEDATIVES

This section also deals with sedation applying to psychiatric conditions Most of the sedatives which were formerly used were hypnotics applied in smaller dosages than those which induce sleep After the introduction of tranquilizing drugs, the use of these diminished considerably

Bromide—Bromide was one of the most common sedatives of the last century It depresses central nervous system function, and in dosages necessary for sedation *it has a cortical action* In smaller doses, bromide causes mental calmness, in

igher doses it produces sleep Bromide is an effective sedative, but, unfortunately n large amounts or if used for a long period of time it can produce lassitude and disturbance of intellectual processes with dullness and faulty memory The lisadvantage of bromide medication is that some patients adapt themselves to the lrug so that larger and larger doses are used to obtain sedation As a consequence, hronic bromide intoxication is not rare Bromide is not prescribed often in psy hiatric practice today and even prior to the introduction of the so-called tranquiliz ng drugs had been almost completely replaced as a sedative by the barbiturates

Barbiturates—For sedative purposes it is customary to use barbiturates in ower dosage than that for sleep induction A large array of barbiturates is on he market of which I would like to mention only a few As hypnotics the bar iturates are divided into long acting intermediate acting short acting and ultra hort acting drugs depending upon how quickly they are able to induce sleep and iow long they maintain their hypnotic effect For sedative purposes long acting r short acting barbiturates or a mixture of both can be used depending upon how long one wishes to maintain sedation Barbital and phenobarbital are used in psy hiatric practice for a long acting sedation amobarbital and butabarbital for inter nediate duration pentobarbital (Nembutal) and secobarbital (Seconal) are the ommon short acting barbiturates

Barbiturates reduce tension and anxiety and therefore are able to influence ome of the clinical manifestations of neurotic and mildly psychotic states In edative doses they do not control massive states of anxiety or excitement or in fluence severe emotional states occurring in the framework of a psychosis or neu rosis

At present the tranquilizing drugs are far superior to the barbiturates in controlling severe emotional states and therefore the use of barbiturates in such conditions has diminished considerably Many patients still receive barbiturates to control some of their neurotic manifestations Here too, however they are be ing replaced increasingly by tranquilizing drugs In psychiatric cases the replace ment is due mainly to the fact that habituation to barbiturates is not uncommon in neurotic and sometimes psychotic patients Habituation to the tranquilizing drugs is observed in some but in general the habituation hazard seems not to be high

Further investigations will have to be made to establish the role of the bar biturates in the treatment of neuroses especially those of the anxiety and tension states in relationship to the tranquilizing drugs Most likely the present trend to treat such patients with tranquilizing drugs will continue especially in cases in which the drug has to be given over a long period Formerly chloral hydrate paraldehyde and scopolamine were occasionally used in psychiatric practice to induce sleep and to sedate excited patients They are still used to induce sleep, for chloral hydrate and paraldehyde are both effective hypnotics but they have not been used as extensively since the introduction of the tranquilizing drugs The unpleasant odor of paraldehyde and taste of chloral hydrate have always limited their use as sedatives Patients who may take these drugs to induce sleep will not take them in smaller quantities more frequently for sedative purposes

The prolonged use of barbiturates or other sedatives in patients with psychi atric disorders should be avoided It is especially bad practice to prescribe these

drugs without knowing in detail the patient's psychiatric condition and to use the medication purely to help the patient symptomatically Sedatives are very important in the treatment of psychiatric patients, but they should be used only after the patient's psychiatric condition is properly assessed In many instances the patient suffering from a psychiatric disorder may need psychotherapy in addition to sedation in order to elucidate and influence the causes of the condition

SELECTED REFERENCES

Borrus, Joseph C Meprobamate in Psychiatric Disorders, M Clin North America, 2, 1957

Bower, W H Chlorpromazine in Psychiatric Illness, New England J Med 251 689, 1954

Cohen, I M Effects of Chlorpromazine in Psychiatric Disorders, Am J M Sc 299 355, 1955

Delay, J, and Deniker, P Thirty eight Cases of Psychoses Under Prolonged and Continuous Treatment, Compt rend du Congrès des Med Alievistes et Neurologistes, Luxembourg, July 21-27, 1952, pp 7-18

Idem Use in Psychiatric Therapy of a Phenothiazine With Selective Central Action, Ann Med Psychol 110 112, 1952

Elkes, J, and Elkes, C Effect of Chlorpromazine on the Behavior of Chronically Overactive Psychotic Patients, Brit M J 2 560, 1954

Goldman, D Treatment of Psychotic States With Chlorpromazine, J A M A 157 1274, 1955

Harris, R Clinical Use of Reserpine (Serpasil) in Geriatrics, Ann New York Acad Sc 59 95 1954

Hoch, P H, Malit [illegible] Clinical Research [illegible]

Hoch, P H New [illegible] Disorders, Bu [illegible]

Hollister, Leo E [illegible] Med 257 170, [illegible]

Hollister, Leo E Allergy to Chlorpromazine Manifested by Jaundice, Am J Med 23 870 1957

Kinross Wright, V Chlorpromazine Treatment of Mental Disorders, Am J Psychiat 111 907, 1955

Lehmann, H E Selective Inhibition of Affective Drive by Pharmacologic Means, Am J Psychiat 110 805, 1954

Miner, R W, editor Reserpine in the Treatment of Neuropsychiatric, Neurological and Related Clinical Problems, Ann New York Acad Sc 61. (Art 1) 1 280, 1955

Moyer, J H, Kinross Wright, V, and Rinney, R M Chlorpromazine as a Therapeutic [illegible] Arch Int Med 95 202 1955

Moyer, [illegible] Evaluation [illegible] 1957

Noce, R [illegible] Management [illegible]

Plummer [illegible] erpine, Ann New York Acad Sc 59 8 1954

Rea, E L, Shea, J and Fozekas, J F Hypotensive Action of Chlorpromazine, J A M A 156· 13, 1954

Selling, L S Clinical Study of a New Tranquilizing Drug J A M A 157 1594 1955

Shaw, C C, and Felts, P W Treacherous Tranquilizers, Am J Med Sc 237 141, 1959

Wallis, R Potentiation of Hypnotics and Analgesics, New York J Med 55 243, 1955

Wilkins, R W Clinical Usage of Rauwolfia, Ann New York Acad Sc 59 36, 1954

Winkelmann, N W, Jr Chlorpromazine in the Treatment of Neuropsychiatric Disorders, J A M A 155 18, 1954

Wortis, J Review of Psychiatric Progress, 1953, Physiological Treatment, Am J Psychiat 110 507, 1954

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Barbiturates reduce tension and anxiety and therefore, are able to influence some of the clinical manifestations of neurotic and mildly psychotic states In sedative doses they do not control massive states of anxiety or excitement or influence severe emotional states occurring in the framework of a psychosis or neurosis

At present, the tranquilizing drugs are far superior to the barbiturates in controlling severe emotional states, and therefore, the use of barbiturates in such conditions has diminished considerably Many patients still receive barbiturates to control some of their neurotic manifestations Here too, however, they are being replaced increasingly by tranquilizing drugs In psychiatric cases the replacement is due mainly to the fact that habituation to barbiturates is not uncommon in neurotic and, sometimes, psychotic patients Habituation to the tranquilizing drugs is observed in some but in general the habituation hazard seems not to be high

Further investigations will have to be made to establish the role of the barbiturates in the treatment of neuroses especially those of the anxiety and tension states in relationship to the tranquilizing drugs Most likely the present trend to treat such patients with tranquilizing drugs will continue especially in cases in which the drug has to be given over a long period Formerly chloral hydrate, paraldehyde and scopolamine were occasionally used in psychiatric practice to induce sleep and to sedate excited patients They are still used to induce sleep, for chloral hydrate and paraldehyde are both effective hypnotics, but they have not been used as extensively since the introduction of the tranquilizing drugs The unpleasant odor of paraldehyde and taste of chloral hydrate have always limited their use as sedatives Patients who may take these drugs to induce sleep will not take them in smaller quantities more frequently for sedative purposes

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siderations involved The older literature refers to the dangers of treating cardiac patients with hypnotics (especially chloral) this erroneous concept is no longer held by most physicians

Addiction—It has been unequivocably demonstrated that barbiturates can produce physical dependence Without question these drugs can also lead to habituation They qualify as truly addicting drugs Although complete information on this point is not yet available regarding recently introduced agents it is probably safest to assume until proved otherwise, that newer hypnotic drugs can also lead to such addiction On the other hand it must be emphasized that *under usual conditions of hypnotic usage, the problem of drug addiction is almost nonexistent with either barbiturates or nonbarbiturates*

Suicidal Attempts—Attempted suicide with barbiturates is a common occurrence Attempted suicide with most of the newer sleeping medications has also been reported In the case of some of these compounds death has occurred Since it is difficult to conceive of a compound with definite hypnotic potency which cannot cause death if taken in sufficient quantities it would seem only a question of time before all of the newer hypnotics have fallen into this same unfortunate category

Tolerance—The development of tolerance to routine nightly doses of hypnotics, frequently discussed, has not been demonstrated conclusively Tolerance to phenobarbital has been studied in epileptics and has definitely been shown to occur In barbiturate addicts however, there seems to be a definite ceiling to this tolerance and its magnitude is by no means as great as that seen with drugs such as morphine

Cost—The older medications such as chloral hydrate and the barbiturates are a good deal cheaper than the newer drugs

THE SEVERAL DRUGS USED AS HYPNOTICS

Chloral Hydrate—One of the oldest drugs available for the purpose of inducing sleep is chloral hydrate It is an effective hypnotic for this purpose and its availability in capsules in recent years has increased its popularity Trichloroethanol, the active metabolite of chloral hydrate, is also an effective hypnotic but it is as yet not available for commercial sale in either liquid or capsule form

Paraldehyde—Paraldehyde is an old and effective agent for producing sleep but has drawbacks in regard to taste and odor It is no longer employed to any great extent except in the management of alcoholics

Barbiturates—The barbiturates are the most frequently prescribed hypnotics and comprise (with chloral hydrate) the most useful medications now on the market In my experience one can get satisfactory results in most patients from either of the two most popular barbiturates (pentobarbital sodium and secobarbital sodium) when these drugs are given in doses of 0 1 or 0 2 Gm The alleged differences in onset of action and duration of effect between these drugs have not obtained in the clinical trials conducted by us Phenobarbital has appeared somewhat less effective and predictable than pentobarbital or secobarbital when given in similar dosage

THE CHOICE OF A HYPNOTIC

Louis Lasagna, M D.

INTRODUCTION

Adult man spends approximately one-third of his life in sleep Whether such behavior is optimal or necessary could be debated, the fact remains that most people consider adequate sleep to be important Experimental studies on healthy young males and casual observation on other populations indicate that sleep deprivation is compatible with essentially normal performance for long periods of time, and that such loss of sleep does not create a cumulative "sleep debt" which must eventually be paid Nevertheless, people who usually sleep well often look and feel below par on the day after a restless night In addition, a significant percentage of the population appears to be awake for variable periods of time on most nights, many of these individuals are bothered by their insomnia by their "tiredness" in the morning, or by both It must be remembered, however, that some people who lie awake for variable periods at night are *not* bothered by this and neither need nor want sleeping pills

CLINICAL CONSIDERATIONS

The physician is off to a good start in managing his patient's insomnia if he first ascertains certain basic pertinent facts These data can be classified into four major categories nature of the sleep disorder, character of the patient's daily activity, past experience with sleeping medications, and general attitude toward medications

Nature of the Sleep Disorder—Some patients have difficulty only in *falling* asleep and, once asleep, need no additional pharmacologic help Other patients have no trouble in falling asleep, but wake up one or more times during the night Still other patients (and in my experience, the majority of insomniacs) have trouble in falling asleep *and* in staying asleep, and for such individuals the optimal drug is one [illegible]
or most of [illegible]
such as "I [illegible]
but in some patients pain is the primary cause of disturbed sleep This latter group may require treatment with appropriate analgesics and will not be considered in this chapter

"average" dose does not work properly Unless the patient rebels at the suggestion, some experimentation with dosage as recommended above is strongly advised If an unsatisfactory *performance does not result after these maneuvers, the newer drugs* may be tried My current order of preference of the new drugs is Noludar, 0 2 to 0 4 Gm , Doriden 0 5 to 1 Gm , Valmid or Placidyl, 1 Gm Because of the *tremendous background of experience with chloral hydrate and barbiturates* and since these standard, cheaper drugs work so well in most patients, I believe the chief value of the newer agents to be their occasional usefulness in case of failure with the older and better known drugs

RATIONAL BASIS FOR NEW DRUGS FOR INSOMNIA

It would be highly desirable to have a uniformly effective hypnotic drug which did not produce hang over, tolerance, addiction, rashes, paradoxical excitation, or other bad effects It seems unlikely that such a perfect somnifacient will be devised In regard to hang over, for example, it is difficult to imagine that any drug capable of combating successfully the intermittent wakefulness which some patients experience throughout the night will 'turn itself off' immediately upon the patient's awakening in the morning If patients demand a sustained hypnotic effect for 8 hours some will in all likelihood have to pay a price for this Furthermore, certain people will probably always abuse drugs, including sedatives Such pessimistic considerations apply to most of the other respects in which the present drugs are deficient None of the new nonbarbiturate hypnotics represent significant advances along these lines The pharmaceutical industry continues to search for better drugs however, and perhaps some progress will be made It *should be stressed, on the other hand,* that at present therapeutic difficulties are relatively minor in the great majority of patients, who can be adequately handled by intelligent use of the drugs currently available

SELECTED REFERENCES

Lasagna, L A Comparison of Hypnotic Agents J Pharmacol & Exper Therap 111 9 1954
Lasagna, L A Study of Hypnotic Drugs in Patients With Chronic Diseases J Chron Dis 3 122 1956
Lasagna, L Across the Counter Hypnotics Boon, Hazard, or Fraud? J Chron Dis 4 552 1956
Lasagna L The Newer Hypnotics, M Clin North America 359 1957
Owens, A H Jr, Marshall, E K, Jr, Broun, G O, Jr, Zubrod C G, and Lasagna L A Comparative Evaluation of the Hypnotic Potency of Chloral Hydrate and Trichloroethanol Bull Johns Hopkins Hosp 96 71 1955
Sessions J T, Jr Minkel H P Bullard J C, and Ingelfinger F J The Effect of Barbiturates in Patients With Liver Disease J Clin Invest 33 1116 1954

Methyprylon —Noludar (methyprylon) is an effective compound which resembles pentobarbital or secobarbital in its effects The dose required for effective use (0 2 or 0 4 Gm) is about double that for pentobarbital and secobarbital

Glutethimide —Doriden (glutethimide) is somewhat similar to Noludar chemically Its effects resemble those of the barbiturates, but it must usually be given in doses of 0 5 or 1 Gm

Meprobamate —Meprobamate (Miltown, Equanil) in doses of 0 4 or 0 8 Gm is satisfactory for some patients in inducing and maintaining sleep

Methylparafynol —Dormison (methylparafynol) is an unsaturated alcohol of rather weak potency Its usefulness in any but the mildest types of insomnia is extremely limited

Ethchlorvynol —Placidyl (ethchlorvynol) is a drug resembling Dormison in chemical structure, but appears more potent than Dormison It must be given in doses of 0 5 or (more often in my experience) 1 Gm for effective activity in patients with insomnia

Ethinamate —Valmid (ethinamate) in my experience has to be given in 1 Gm doses in order to achieve therapeutic effectiveness in the majority of patients

Antihistaminics —There are many across the counter hypnotics available on the market, most of which contain one or another antihistaminic The most common of these antihistaminics is metapyrilene, which is relatively ineffective as a hypnotic in the recommended doses Other antihistaminic agents such as Benadryl are capable of inducing drowsiness in some patients but they are not often prescribed in adults specifically for this purpose and are not as predictable or effective as the best barbiturates

"Tranquilizers"—Most of the new potent "tranquilizing" agents are sedatives, but they are not usually employed as hypnotics Their use as tranquilizers is discussed in another chapter

HOW TO USE HYPNOTICS

If a patient has difficulty only in falling asleep, a recommended practice is to prescribe chloral hydrate in a dose of 1 Gm If, for some reason the patient objects to chloral hydrate, secobarbital or pentobarbital, 0 1 Gm , can be used If the patient's only difficulty is awakening during the night, one can employ several therapeutic maneuvers One can prescribe chloral hydrate to be taken if the patient awakens in the middle of the night or very early in the morning An alternative is to prescribe secobarbital or pentobarbital in doses of 0 1 Gm at bedtime to *prevent* waking during the night If the patient has difficulty *both* in going to sleep *and* in staying asleep, one should also prescribe secobarbital or pentobarbital in dose of 0 3 Gm

In each of the instances mentioned above, the dose of medication should be doubled if the patient does not achieve enough hypnotic effect, or halved if the patient has too much residual effect Occasionally the dose may even be tripled, but this is not recommended for most patients (With higher doses the problems of tolerance, physical dependence, and residual sedation become serious considerations) *It is important not to switch from one drug to another merely because the*

Table 14 Comparison of Results From Various Methods of Treatment for Epilepsy*

	No of Patients	Grade of Improvement (Per Cent)					Severe Toxic, or Fatal Reaction to Treatment
		4 (Seizure Free)	3	2	1	0	
Ambulatory Treatments							
No specific treatment							
Trousseau	150	13	–	–	–	–	–
Herpin	58	50		–	–	–	–
Bromides							
Turner	366	24	–	28	–	–	–
Pollock	85	72	–	–	–	–	–
Arieff	14†	73	–	–	–	–	–
Ketogenic diet							
Wilkins	30	27	–	–	–	–	–
Keith	190	35	–	18 4	–	46 3	–
Peterman	123†	–	80	–	–	20	–
Phenobarbital							
Lennox	766	–	65	–	–	–	–
Arieff	48†	90	–	–	–	–	–
Ives	111†	27	19	–	–	–	–
Diphenylhydantoin							
Putnam and Merritt	118	58	27	5	–	10	–
Yahr and others	50†	15	–	9	–	–	–
Boller	520†	23	–	24	–	15	–
Ives	92†	20	28	–	–	22	–
Phenantoin							
Kozol	115†	–	60	–	–	40	–
Lennox	30†	–	20	–	–	–	–
Loscalzo	67†	32	50	–	–	18	–
Ives	41†	10	29	–	–	22	–
Glutamic Acid‡							
Price and others	8†	12	38	25	–	25	–
Zimmerman and others	7†	70	15	15	–	–	–
Trimethadione‡							
Lennox	145†	33	30	21	0	16	0
Ives	44†	7	29	–	–	32	–
Phenacemide							
Tyler and King	1,562†	37	–	31	–	32	21
Davidson and Lennox	178†	3	19	24	–	–	15

THE CHOICE OF AN ANTICONVULSANT*

Tracy Jackson Putnam, M D.

INTRODUCTION

The incidence of epilepsy is closely comparable to the incidence of diabetes, each affecting approximately one million people on this continent At present, epilepsy probably entails more total disability and economic loss than diabetes, but it attracts far less study and intelligent understanding from the majority of doctors, and research in the field is poorly endowed A revolution has occurred in treatment of both diseases in diabetes beginning about 35 years ago, in epilepsy about 20 years ago But whereas every practitioner has some knowledge of the fundamental principles of treatment of diabetes and attains a high proportion of relief of symptoms in the great majority of cases, even specialists in neurology are usually fatalistic about epilepsy and tend to stick to the exclusive use of one or two drugs rather than analyzing the individual patient's needs As a result, there is an enormous difference in the proportion of patients maintained seizure free from clinic to clinic—as low as 20, as high as 77—so that it seems likely that a widespread use of methods now available might return about half a million epileptics to employability and restoration of full citizenship

CLINICAL APPLICATIONS

Until about 1936, it was by no means clear that epilepsy was a disorder to be treated primarily by drugs At that time the two prevailing schools of thought held that it was a form of conversion hysteria best treated by psychotherapy, and that it was the result of scars of the brain, theoretically best treated surgically Largely as a result of the work of Lennox and of Gibbs, it then became clear that there was uniformly a demonstrable electrical disturbance in the cortex during an attack, more or less specific for the attack, often detectable in some degree in the interseizure period Further, it became clear that drugs and physiologic alterations, for example, in the acid base equilibrium might have a profound effect both on the dysrhythmia and on the seizures

*The expenses of the investigation upon which this chapter is founded were borne in part by the Tracy J Putnam Foundation and the Foundation for Research, Inc

About the same time, also in my former clinic at the Boston City Hospital the first nonsedative anticonvulsant drug, diphenylhydantoin, was selected by animal experiment and tested clinically The conception of such a drug and of its general configuration antedated this period by several years, as I have described elsewhere, but the actual accumulation of promising materials and the experiments were begun in 1936, and published the following year The announcement was greeted with a torrent of abuse Up to that time, the drugs used in treatment of epilepsy, chiefly bromides and phenobarbital, were discovered empirically, and textbooks of pharmacology stated flatly that epilepsy had to be treated, if at all with sedatives and that there was little choice between the barbiturates

Once the possibility was demonstrated that there could be a nonsedative anticonvulsant the requirements of the ideal drug seemed clear It should be effective in controlling seizures and the underlying dysrhythmia, it should be non toxic in therapeutic doses, and long retained in the body Even at that time it seemed likely that at least two different types of anticonvulsants should be sought one type designed like diphenylhydantoin to control excessive rapid dysrhythmia the other like ketosis, and later glutamic acid, to control the slow-wave dysrhythmia of petit mal psychomotor episodes, and periodic dullness

At present about 14 effective drugs are available, none of them ideal Some of these are apparently harmless, fatality rates approaching 1 per cent have followed administration of others in some series The practitioner and even the specialist is apt to find himself confused by the plethora, and reference to the literature is not particularly helpful The majority of published reports fall into two groups those which uphold the virtues of old methods of treatment such as the use of bromides surgery, phenobarbital and the ketogenic diet, and those which extol the virtues of individual new drugs In the latter instance, the investigator uses the new drug on patients who have been inadequately treated or not at all Often the term improvement" is used in an elastic manner, and it appears that some of the drugs recommended may control seizures only at the cost of disabling symptoms such as drowsiness and depression in the cases of bromides, pheno barbital and phenacemide (Phenurone), or at some risk of severe or fatal toxic

Table 15 Reported Effect of Various Medications on Specific Types of Attacks

	Proportion of Patients Relieved (in Per Cent)			
	Grand Mal	Petit Mal	Psychomotor	Focal
Phenobarbital	27	?	20	?
Phenytoin	56	35	62	50
Phenantoin	32 56	15	50	56
Glutamic acid	0	12	70*	0
Trimethadione	6	28	?	?
Paramethadione	9	?	9	?
Phenacemide	62*	29*	51*	?
Primidone	57	?	4	?
Metharbital	30	17	?	?
Phensuximide	0	22	20	?
Acetazolamide	50*	40	?	0
Peganone	65	47	36	?
Prenderol	?	60*	?	?
Tetrantoin	53	0	0	60

*Greatly benefited

Spirodon							
Putnam and Jacobs	66	14	44	16 5	9	16 5	-
Standard Treatment							
Ives	212	31	-	-	-	-	
Yahr and others	319	48	-	37	-	-	
Putnam and Rothenberg	75	56	4	7	33	-	
Radical Treatments							
Excision of cortical scars							
Penfield	59†	25	30	14	12	18	1 3
Excis on of motor cortex							
Pilcher and others	41‡	20	30	21	-	-	4
Intensive medical treatment							
Putnam and Rothenberg	25	64	20	16	-	-	0
Standard and/or intensive treatment							
Putnam and Rothenberg	75	77	11	12	-	-	0

*Modified from Putnam, T J, and Rothenberg, S F Results of Intensive (Narcosis) and Standard Medical Treatment of Ep lepsy, J A M A 152 1400, 1953 References in original article

†Selected patients The basis of selection was not always clear

‡Effect on petit mal or psychomotor attacks

*Table 16 Structure and General Properties of Common Anticonvulsants**

(Refer to Fig 6 for key to structural formula)

	Range of Daily Dose for Adult (Gm)	R	R_1	R_2	Usual Use	Chief Toxic Symptoms
Barbituric Acids						
Phenobarbital	0 1 0 4	C_2H_5	C_6H_5	H	Grand mal focal seizures	Sedative increases psychomotor activity, rashes deaths from suicide
Mephobarbital	0 1 0 4	C_2H_5	C_6H_5	CH_3	Similar to phenobarbital	Similar to phenobarbital
Metharbital	0 1 0 4	C_2H_5	C_2H_5	CH_3	Similar to phenobarbital better for petit mal	Similar to phenobarbital
Primidone	0 25 1 5	CH_3	C_6H_5	CH_3	Recommended also for petit mal	Similar to phenobarbital rare bone marrow depression
Hydantoins						
Phenytoin (Diphenylhydantoin)		C_6H_5	C_6H_5	H	All types of seizures	Ataxia headache, hypertrophy of gums, hypertrichosis Probably safest anticonvulsant 1 questionable fatality
Phenantoin (Ethylphenyl N methyl hydantoin)	0 2 0 6	C_2H_5	C_6H_5	CH_3	Grand mal, focal	More sedative than phenytoin bone marrow depression frequently reported 8 fatalities
Tetrantoin (2 tetralone hydantoin)	1 0 7 0	2, tetralone		H	Grand mal, focal	New drug, apparently low toxicity
Ethotoin (3, 4 dihydro 2 [1H] Naphthalenone)	2 0 3 0	C_6H_5	H	C_2H_5	All types of seizures	New drug Rashes, vomiting, drowsiness, agranulocytosis, 1 fatality
Oxazolidinediones						
Trimethadione	0 6 1 2	CH_3	CH_3	CH_3	Petit mal, psychomotor	Sensitiveness to light drowsiness bone marrow depression 1 fatality reported
Paramethadione	0 6 1 2	CH_3	C_2H_5	CH_3	Similar	Similar
Succinimides						
Phensuximide	0 5 2 7	H	C_6H_5	CH_3	*Petit mal psychomotor*	*Drowsiness*
Methsuximide	1 2	CH_3	C_6H_5	CH_3	Psychomotor	Rash drowsiness ataxia
Acetylureas						
Phenacemide	0 5 2 0	H	C_6H_5	H	All types of seizures	Personality change bone marrow depression liver damage 4 fatalities reported
Miscellaneous						
Acetazolamide	0 75	2 acetylamino 1 3 4 thiadiazole 5 sulphonamide			All types reports of effectiveness vary widely	Bone marrow depression 2 fatalities
Diethyl propanediol	4 0 8 0	2 2 diethyl 1 3 propanediol			Grand mal	Drowsiness new drug

*Modified from Toman J E P and Taylor, J D Mechanism of Action and Metabolism Anticonvulsants Epilepsia 1 31 1952

reactions, such as those reported following the use of phenantoin, phenacemide, phethenylate, trimethadione, and paramethadione A summary of results of the use of various methods of treatment is given in Table 14

From data such as these and certain pharmacologic tests, it has become traditional to use some drugs first against certain types of seizures, others against other types, as summarized in Tables 15 and 16 As will be seen below (especially from Table 18 and the description of the rapid determination of optimum medication), these traditional usages are approximations Actually, the optimum drug or combination for the individual patient can be found only by experimentation, preferably systematic, with that patient For what it is worth, however, the *data in Table 15 have been collected from the literature The statistics shown* are for the most part extremely crude and have not been collected in any uniform manner The majority of papers written on this subject are impressionistic and give no quantitative data

GENERAL PHARMACOLOGIC CONSIDERATIONS

Pharmacologic Requirements of Anticonvulsants.—Soon after the introduction of diphenylhydantoin, I made a study of the requirements of anticonvulsants on the basis of those found effective among the first substances tested The following attributes seemed clear

1 The substance should have a high solubility in fats and a low solubility in water at neutrality

2 It should contain one or more phenyl or related nuclei in a terminal position

3 Usually if any other group is attached to this terminal nucleus, the substance becomes inactive

4 Adjacent to the terminal, phenyl or similar nucleus, or separated from it by not more than 2 radicals (usually of aliphatic character) is a "reactive" group containing a double bond, usually O—O, which is not terminal Other "reactive" groups which occurred in the first series were CNOH, SO_2, SO, and the benzoxazole linkage

5 There may be other "reactive" groups in the molecule, but if so they are usually separated by "nonreactive" C or N groups

6 Double bonds are found only in the "reactive" groups, with rare exceptions

7 The presence of CH_2CH_3 groups or longer similar chains attached to the "reactive" group causes the appearance of sedative and toxic effects, as would be expected on general pharmacologic principles (Richardson's law)

8 *Linkages through an —O— atom,* the presence of furyl nuclei, or of a terminal $—NH_2$ conferred toxic properties on the substances in which they were found

9 In only one effective substance (diphenyl acetic acid) was a terminal —COOH group found

10 There was only one alcohol in the series, phenyl glycol which showed the expected sedative action

11 The only ring structures containing "reactive" groups found in the origi-

*Table 17 Summary of the Fate of Some Anticonvulsant Drugs**

Name	% Excreted Unchanged in Urine	Metabolite	% Excreted as Metabolite in Urine	% of Drug Unaccounted for	Species
Phenytoin	10	—	—	90	man
	3	5, 5-diphenyl hydantoic acid 5, 5 diphenyl-α aminoacetic acid	4 23	70	dog
	1 4	5, 5 diphenyl hydantoic acid 5, 5 diphenyl α aminoacetic acid	1 5 10 27	65 70	man dog
	0	—	—	100	rat
Phenantoin	0	5 ethyl 5 phenyl hydantoin (Nirvanol)	16 20	80	dog
	0	5-ethyl 5 phenyl hydantoin (Nirvanol)	2 22	80	man
Nirvanol	15	5-ethyl 5 phenyl hydantoic acid 5 ethyl 5 phenyl-α amino acetic acid	1 30	55	dog
Phenobarbital	11 25	?	—	75 90	man dog
Metharbital	2 3	barbital	44	50	dog
Mephobarbital	0	phenobarbital	4	95	dog
Trimethadione	2	?	—	98	man
	1 2	?	—	98 99	rat
Phenacemide	0	phenolic compounds	30 40	60 70	man
	0	phenylacetic acid and/or derivatives	20	80	rat

*Adapted from Toman J E P, and Taylor, J D Mechanism of Action and Metabolism of Anticonvulsants, Epilepsia 1 31, 1952

After a preliminary study to minimize the likelihood of overlooking a tumor or other progressive or operable lesion, the following principles should be observed

1 Relatively well known and nontoxic drugs should be preferred to dangerous or untried ones In respect to serious permanent toxic effects, diphenylhydantoin is probably the safest drug, with phenobarbital in close competition Phenobarbital is often used successfully as a suicidal agent and practically always produces some sedation or depression in effective doses Alarming or fatal reactions have been reported from the use of trimethadione (Tridione), paramethadione (Paradione), phenacemide (Phenurone), and phenantoin (Mesantoin), the risk apparently increasing in about that order In recent years, deaths from this cause have practically ceased to be reported from the 3 first named drugs, suggesting that the toxicity may have been due to some impurity in earlier batches, but Kozol recently report· ... Mesantoin Close laborator ... ounts) is essential when ... Schwab have pointed out, this materially increases the patient s economic burden

2 Treatment should always be started with the most familiar, thoroughly

nal series were the barbituric acid and hydantoin rings (but several o... since been demonstrated)

Most of these conclusions have been well sustained in the intervening years as will be seen in Fig 6 and Table 16 (both modified from Toman's valuable article, 1952)

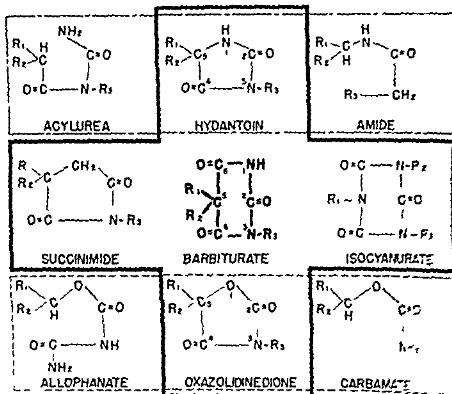


Fig 6—Structural rel... cross closed ring s... three major groups ... hydantoins Bottom r... Right vertical row ... Toman J E P and Epilepsia 1 31 1952

Table 17 from the same source indicates the fate of some of the ... anticonvulsants in the human and animal body This same art... excellent review of the pharmacologic literature and references ... be repeated here

A DESIGN FOR THE USE OF DRUGS FOR CONTROL OF ...

Principles —A systematic program of trial and selection ... drugs was foreshadowed in 1939, and more fully developed ...

ness are predominant Milontin, glutamic acid, trimethadione, paramethadione, Celontin, and phenacemide are preferred next, in that order Amphetamine may be tried Vigorous exercise should be required of the patient

7 Patients should be instructed to *report the occurrence of one or a few* seizures, and the dose of the drug they are using ordinarily should then be in creased, or a new agent should be added In the long run, especially in growing children, some drug tolerance may gradually develop, and the tolerance dose should be readjusted every year or when symptoms recur

8 The use of adjuvant therapy, such as exercise, the use of ataraxics as indi cated, avoidance of strain and fatigue and deleterious activities and simple psycho therapy are almost always advisable Extreme moderation in the use of alcohol *must be required*

9 Surgical measures should be considered only when adequate standard medical treatment, as defined, and, perhaps, a trial of intensive treatment, as de scribed briefly below, have failed Similar medical measures usually have to be carried out after cortical extirpation and only sometimes are more effective after ward than they were before

Approximate observance of these rules constitutes what has been termed the "standard treatment " A comparison of the results of such a procedure, in com parison with those restricted to individual drugs, and also with certain drastic treatments, namely, operative treatment of focal seizures the ketogenic diet and the intensive or narcosis treatment, is given in Table 14

Rapid Determination of Optimum Medication—The rigid application of these principles sometimes imposes an onerous task on the physician and patient In a certain proportion of cases, this period *of experimentation becomes intolerable* It is particularly likely to become so when a wage earner develops seizures which may deprive him of his job if they are not promptly controlled, or when a child s education is imperiled by convulsions Under such circumstances, a rapid de termination of optimum medication may be carried out, as described by Putnam, Rothenberg, and Bercel in 1954 Briefly, this consists in hospitalizing the patient for about 2 weeks At the outset, all medication is withdrawn and an electro encephalogram is taken as a base line Then each day, a large dose of one of the anticonvulsants—each day a new one—*is given and an electroencephalogram* is taken 2 or 3 hours later If the patient has seizures or develops drowsiness, vertigo, confusion, or other toxic manifestations, symptomatic treatment is given At the end of the period all of the electroencephalographic records are compared *It is* usually perfectly clear which drugs are effective, which ineffective and which toxic Table 18 shows the drugs tried the dosages used, and the outcome

Drugs which are ineffective or produce toxic manifestations in the test are seldom found clinically useful An exception is phenytoin Those which improve the electroencephalographic record are *usually* but *not* always well tolerated and effective in practice The optimum dose for the individual must be determined after completion of the test Further details should be read in the original article

Intensive or Narcosis Treatment—In about 40 per cent of patients, no am bulatory treatment so far devised is successful Under such circumstances, it is proper to consider one of the drastic treatments, such as the use of *the ketogenic*

tested and reliable drug and newer, less known drugs should be added or substituted only for clear cause Diphenylhydantoin has displaced phenobarbital in this position for the majority of patients, regardless of type of seizure The dose is usually 0 2 Gm daily and it is gradually increased at the rate of 0 1 Gm weekly Diphenylhydantoin in oil should be used when gastric irritation is produced by the sodium salt A special tablet is available for children, or the tasteless oily suspension may be mixed with food A second choice is usually Mesantoin or phenobarbital in patients suffering from grand mal Tridione, Paradione, or Milontin in those suffering from petit mal, but some of the newer drugs are now strong competitors

3 The dose of each drug used should be increased gradually until symptoms of overdosage are produced then it should be reduced slightly It is now clear that with practically all drugs of this group, individual tolerances vary widely, some patients tolerating 3 or 4 times as much as others per unit weight Almost always, the best therapeutic dose is close to the toxic dose

Hypertrophy of the gums, which occasionally occurs as a minor toxic effect of phenytoin therapy, can almost always be controlled by vigorous massage, preferably perhaps with hydrocortisone ointment The administration of ascorbic acid and of antihistamines may also be tried, they are not very successful in my experience Amphetamine in doses up to 5 mg or, better pipradrol (Meratran) in doses up to 15 mg may be given in the morning to combat the drowsiness caused by some drugs in the series Toxic rashes and leukopenia are sometimes controlled by the use of cortisone Unless a drug under trial is clearly toxic or useless it should be continued until the next drug to be evaluated is being given in reasonable doses

4 The method of increasing the dose of each drug gradually to the tolerance level adding new ones to the regimen if the ones previously used are inadequate and gradually discarding those obviously ineffective or deleterious, should be continued until the seizures are controlled or until use of all the available drugs has been tried About 3 months are required for thorough trial of each new drug or combination of drugs This period of experimentation, which is often tedious and sometimes almost intolerable, may be shortened by use of the method of rapid determination of optimum medication to be described briefly below Clearly this has some disadvantages also

5 The use of phenobarbital and, probably also, of primidone (Mysoline) and Mesantoin usually should be avoided if spike and dome or psychomotor' complexes are present in the electroencephalogram or if definite, typical petit mal, dullness, or psychomotor manifestations are present Phenobarbital, especially sometimes seems to convert typical petit mal attacks into psychomotor outbursts, suppressing also the "spike" in the electroencephalogram The use of trimethadione, paramethadione or glutamic acid should be avoided except in cases in which some or all of these manifestations are present Use of one of these latter drugs usually should be accompanied by a maximal tolerance dose of one of the hydantoins (diphenylhydantoin, Mesantoin, Spirodon)

6 Diphenylhydantoin, when the dosage is pushed to the tolerance level, is the drug of choice in patients in whom psychomotor phenomena or periodic dull

promazine or one of its analogs The barbiturates and primidone should be avoided, as accidents have occurred following their use Other anticonvulsants have not been tried The principal problem is nursing care, and this makes the treatment extremely expensive It is, however, often effective when other measures fail Of 35 patients treated, 21 are seizure-free, a few others somewhat improved The treatment was given twice in 2 cases Further details should be read in the original article

RATIONAL BASIS FOR NEW DRUGS FOR EPILEPSY

No universal anticonvulsant has yet been found Particularly urgent is the need for drugs which will control petit mal, psychomotor seizures, periodic dullness, epileptic psychoses, and dysrhythmias of the slow wave type A small proportion of tantalizing good results have been obtained with starvation, the ketogenic diet, acidifying agents, and glutamic acid, which presumably act through similar mechanisms Perhaps the hope that led to the development of glutamic acid, namely, that we might synthesize and render clinically useful some of the "ketone bodies" presumably produced in the course of fasting and the ketogenic diet, may yet be realized

Aside from control of the dysrhythmia, symptomatic treatment of the epileptic is entering a new phase This is of particular importance for the reason that with the advent of more effective forms of anticonvulsive treatment the incidence of (or disclosure of) posttherapeutic disturbed states is also increasing Some success has been obtained with chlorpromazine and similar drugs, also with the meprobamate group But much remains to be done

SELECTED REFERENCES

Abbott, J [illegible] Drugs [illegible] n) in [illegible] eases [illegible] lepsy [illegible] J A

Ives, E [illegible] 147 1332, 1951

Kozol, H The Place of Mesantoin in the Treatment of Epilepsy Efficacy vs Toxicity (Read before the American Academy of Neurology, April 25, 1957)

Lennox, W G The Petit Mal Epilepsies—Their Treatment With Tridione, J A M A 129 1069, 1945

Livingston, S, and Petersen, D Primidone (Mysoline) in the Treatment of Epilepsy Results of Treatment of 486 Patients and Review of the Literature, New England J Med 254 327, 1956

Lombroso, C T, David [illegible] rther Evaluation of Acetazolamide [illegible] A 160 268, 1956

Merlis J K Medical [illegible] 245, 1951

Merritt H H, and Pu[illegible] Treatment of Convulsive Seizure [illegible] Neurol & Psychiat 42 1053, 1939

Merritt, H H, and Putnam, T J Experimental Determination of Anticonvulsive Activity of Chemical Compounds, Epilepsia 3 51, 1945

Merritt, H H, Putnam, T J, and Bywater, W G Anticonvulsant Action of Sulfoxides and Sulfones, Arch Neurol & Psychiat 54 319 1945

Meszaros, A F, and O Reilly, P O Relation of Chlorpromazine to Epilepsy, Dis Nerv Syst 17 159, 1956

*Table 18 Relative Effectiveness of Various Drugs as Revealed by Rapid Determinations**

	Dose (Gm)	Number of Cases	Best	Second	Made Worse	Toxic Waves
Phenytoin	1 0	47	14	7	2	0
Trimethadione	2 0	47	4	8	5	1
Phenantoin	1 0	47	4	6	4	2
Phenobarbital	1 0	40	9	6	2	4
Phenacemide	7 5	33	3	0	11	3
Paramethadione	2 0	35	5	4	7	0
AC 268	2 0	27	3	1	5	0
Phethenylate	2 0	20	0	2	4	0
Phensuximide	3 5	19	1	1	2	0
Glutamic acid	30 0	18	0	2	0	0
Primidone	1 5	17	2	1	3	–
Tetrantoin	6 0	9	3	0	0	0
Celontin	3 0	2	0	1	1	0
Peganone	2 5	2	0	0	0	0
Chlorpromazine	0 1	1	0	0	0	0

	Number of Cases Improved	Best or Second			Best or Second Dysrhythmia Types†				
		Grand Mal	Petit Mal	Psychomotor†	1 2 C/S	3 4 C/S	5 7 C/S	Spike	Rapid
Phenytoin	21	20	2	6	1	6	9	2	2
Trimethadione	12	10	2	1	2	5	4	1	0
Phenantoin	10	3	2	2	0	0	7	1	0
Phenobarbital	15	15	2	3	4	6	7	0	2
Phenacemide	3	3	0	1	1	0	1	0	0
Paramethadione	19	6	1	2	1	5	3	2	0
AC 268	4	0	0	1	1	0	0	0	0
Phethenylate	2	2	0	0	0	1	0	1	0
Phensuximide	2	2	1	0	0	1	0	0	1
Glutamic acid	2	2	0	2	0	1	0	0	0
Primidone	3	3	2	0	0	2	1	0	0
Tetrantoin	3	3	1	0	0	2	1	0	0
Celontin	2	1	0	1	0	1	1	0	0

*Modified from Putnam, T J, Rothenberg, S F, and Bercel, N M Rapid Determination of Optimum Medication in Recalcitrant Cases of Epilepsy, A M A Arch Neurol & Psychiat 72 169, 1954

†When more than one type was improved, in the same case, all are listed

diet, surgery, or the intensive or narcosis treatment The published results of such procedures are summarized in Table 14, it should be remembered that they are applied presumably only to severe cases unrelieved by simple ambulatory treatment Naturally, the first two are outside of the scope of this paper, but a note on the intensive treatment may properly be added here

The intensive or narcosis treatment was first described by Putnam and Rothenberg in 1953, although something resembling it had been used sporadically by others before It consists in giving massive doses of phenytoin—usually 4 Gm per day—for 4 days The first doses are given by mouth, the patient then falls into a deep sleep If he can be aroused sufficiently, the same dose can be given for the remaining days, it may also be given by suppository or intravenously About 2,000 ml of 5 per cent glucose in saline is given by vein daily if the intake drops below 1,000 ml The patient is fed if he is awake, but the development of a ketosis is desirable He is given inhalations of 5 per cent CO_2 in oxygen for 10 minutes every hour, by mask He should receive about 600,000 units of penicillin daily Other sedatives may have to be given, of which the best seems to be chlor-

THE CHOICE OF A SKELETAL MUSCLE RELAXANT

Edward B Schlesinger, M D

INTRODUCTION

The theoretical basis for the use of muscle relaxants is attractive and sound Muscle splinting or spasm is a common sequential response to many wear and tear syndromes of the motor apparatus True spasticity is a major and crippling sign of central nervous system disorders Any attempt at amelioration of these two entities by drugs with central or peripheral neuromuscular effects is physiologically well founded

In the recent past the field has suffered from confusing clinical data This confusion was a manifestation of the varying definitions of the underlying neuromuscular abnormalities, and a consequent lack of communication between clinical investigators Spasticity, muscular spasm rigidity, and involuntary movement were not strictly separated or defined This led to unrealistic goals in comparing results in clinical experiments, and to inevitable disillusionment for many clinicians A more widespread agreement as to the fundamental nature of the clinical states under study has been of inestimable value in adequate interpretation of drug effects

Compounds for testing have come along in unprecedented numbers in recent years Of topical interest is the fact that many of the so-called tranquilizers in such vogue today are related to muscle relaxants in certain critical dosage ranges At least one conspicuously popular drug of this series (Miltown) was a serendipitic outcome of muscle relaxant investigation Since many of these compounds are presented as muscle relaxants it is important to emphasize their status Laboratory protocols demonstrate unequivocally that the drugs have the claimed effects in animal experiments (at certain dosage levels) Nonetheless in the human being the muscle relaxant effect either cannot be obtained at reasonable oral dosage levels or is masked completely by more pronounced effects which appear at ordinary dosage levels These latter effects are of debatable definition but fall within the realm of soporific, sedative or anxiety buffering

CLINICAL CONSIDERATIONS

Presuming a preparation which is characterized by some degree of efficient muscle relaxant effect is available the present day usefulness of such a drug might be outlined as follows

Penfield W

Putnam T J and Merritt H H The Chemistry of Anticonvulsant Substances Arch Neurol & Psych at 45 505 1941

Putnam T J and Merr tt H H

Putnam

Putnam

M A Arch Neurol & Psych at

Toman J E P and Taylor J D Mechan sm of Act on and Metabol sm of Ant convulsants Epilepsia 1 31 1952

Tyler M W and King E Q Phenacemide in the Treatment of Epilepsy J A M A 147 17 1951

Z mmerman F T Burgemeister B B and Putnam T J Effect of Glutamic Acid on Mental Funct oning in Ch ldren and Adolescents Arch Neurol & Psychiat 56 489 1946

a far more complex entity than either muscle spasm or spasticity Its susceptibility to drugs which primarily affect neuromuscular conduction is of an extremely low order Therefore true muscle relaxants have no real place in the clinical therapy of Parkinson s disease The antihistaminics, when they produce a useful effect upon tremor and rigidity, manifest their action by their atropine like properties rather than as muscle relaxants Drugs of the tranquilizer series exert their beneficial effect when present by allaying anxiety and buffering the patient against tension creating stimuli which load performance unfavorably

Involuntary Movements Such as in Athetosis and Dystonia—*In so far as the* individual case is characterized by a concomitant moiety of spasticity there may be a proportionate slight improvement in the patient s motor efficiency The actual involuntary movement, however, will not be affected short of paralyzing doses The fact that varying drugs of the tranquilizer series may favorably alter *the ultimate efficiency of these patients has led to the misapprehension that their* action is therefore muscle relaxant per se The improvement in motor efficiency and performance really lies in the reduction of anxiety and its load of performance rather than in a direct effect on the underlying involuntary movement

THE SEVERAL MUSCLE RELAXANTS

The various muscle relaxant drugs characteristically act at different levels *of the neuromuscular system*

True Muscle Effect—Quinine is, perhaps, the best example of drugs of this series although it has other actions It is useful in the treatment of entities such as night cramps, restless legs and similar states of probable neurovascular implication However it is ineffective in the treatment of muscle spasm or spasticity The antihistaminics are equally effective in the treatment of so called night cramps

Myoneural Junction Effect—Curare a quaternary ammonium salt is the classic example of a drug which achieves muscle relaxation by altering the myoneural junction It is effective predictable and controllable but unfortunately only by the intramuscular or intravenous route Aqueous solutions such as used in anesthesia afford graded relaxation of predictable duration Oil emulsions of curare are limited in their application The intramuscular route of administration along with the need for constant surveillance of the patient makes their use onerous and hazardous except under strict hospital conditions

Drugs With More Central Effects—Most of the remaining drugs in use seem to act by their blocking action on fairly complex interneuronal systems Some in addition have complex effects at other levels making it possible to classify them *with anticonvulsive sedative or anxiety relieving drugs* Nevertheless their action as muscle relaxants is chiefly based on their effect on interneuronal systems within the spinal cord

CLINICAL AREAS OF USEFULNESS OF MUSCLE RELAXANTS

Muscle spasm

The enhancement of conventional physiotherapeutic measures for the relief of muscle splinting and restoration of range of motion as in

Relief of Muscle Spasm or Splinting.—The entity clinically designated as muscle spasm is an integral part of many of the common wear-and-tear syndromes of everyday practice The term is loosely used, but roughly it may be defined as a state of transient muscle contraction not amenable to voluntary control, characterized by resistance to stretch and usually associated with pain on attempted extension Clinically the picture is well recognized. It may be a muscle response to irritation, whether inflammatory or traumatic It may be reflex in origin and secondary to pathologic conditions, visceral or somatic, of like segmental neural connection

Kellgren, Wolff, and others have shown that this latter type of muscle spasm may be perpetuated after cessation of the initiating stimulus and may thus present a major treatment problem The various lesions which together make up the low-back syndrome are excellent examples of the importance of the problem of muscle spasm in treatment The initiating trauma or etiologic agent is followed by muscle splinting as a protective measure Pain enhances the splinting, which in turn is followed by more severe pain and further muscle spasm The vicious cycle is self perpetuating Whether the intense pain is at least partly ischemic in origin is not fully understood Dramatic relief may be afforded by any agent which tends to interrupt and break up the cycle of splinting and pain There are many traditional measures, all of which have some rational and serve their purpose at times admirably These include heat, traction, ethyl chloride spray, procaine or saline injections, and heavy sedation

Spasticity.—Spasticity is characterized chiefly by loss of graded central control of reflex activity Its outstanding feature is the hyperactive stretch response The so called adductor spasm the scissors gait, and the contracted Achilles tendon are common manifestations of spasticity Prolonged spasticity, without adequate range of motion, inevitably leads to contracture and fibrosis which, at their end point, can be affected only by surgical procedures and then with considerable sacrifice The basis of logical physical therapy is to preserve range of motion to allow normal patterns of motor function and, thus, to improve efficiency and prevent contractions Anything which will assist such therapy has a sound basis

Muscle relaxant drugs which act by damping hyperactive stretch response can permit more effective range of motion exercises or voluntary activity They have a theoretical place in the management of lesions of the central nervous system characterized by spasticity However, where ataxia is a concomitant feature, the action of muscle relaxants is often paradoxical For example, the ataxic multiple sclerosis patient uses his spasticity as a sort of long leg brace, and, when it is in any degree diminished, he may feel he has lost efficiency of gait

Rigidity.—Rigidity is a much more complex mechanism than either muscular spasm or spasticity and is characterized both by the release of certain neuromuscular reflexes from central gradation and by simultaneous innervation of agonists and antagonists It is therefore, not surprising that the effect of muscle relaxants is most inefficient and clinically disappointing

Parkinson's Disease.—Rigidity along with tremor and akinesia form the triad of abnormal mechanisms upon which the crippling disability of parkinsonism is based It is natural that, because of the apparent tightness of muscles muscle relaxants have been used in an attempt to allay rigidity As stated before, it is

of the mephenesin series, except in unusually susceptible patients, have no, or almost no, relaxant effect when taken by mouth and can be considered chiefly analgesic Drugs of the meprobamate series cannot be expected to afford true relaxation of either muscle spasm or spasticity in doses which have obvious ataractic effects The one area where there may be a dramatic response is in the dystonic and athetoid groups Short of the creation of drowsiness by their soporific effect, the drugs seem to insulate or buffer the patient's motor performance from the impact of his emotional environment This may lead to a clinically perceptible increase in efficiency of performance, but such a change is completely unrelated to a true muscle relaxant action

SUMMARY

Muscle relaxants as a group have the dignity of being endowed with excellent sherringtonian principles in their application to the treatment of muscle spasm and spasticity Unfortunately, there are no adequate preparations for oral use which can be counted upon to achieve a reliable muscle relaxant effect It is necessary, therefore, to fall back on representatives of the series which are only useful by the intravenous and intramuscular route This severely limits the application of drugs in everyday therapy There seems, however, little doubt that the present awareness of the potential usefulness of such drugs will lead to the eventual synthesis of more efficient preparations

SELECTED REFERENCES

Arieff A J Pyzik S W, and Finkle, J R Inefficacy of Flexin Therapy for Spasticity Due to Spinal Cord Injuries, Illinois M J 112 169 1957

Burns J J Yu, T I Berger, L, and Gutman A B Zoxazolamine Physiological Disposition Uricosuric Properties Am J Med 25 401, 1958

Cohen T Nephropathy Associated With the Oral Administration of Zoxazolamine (Flexin), [illegible]

Current [illegible] Disease, New Eng

Domino [illegible] and Clinical Ef[illegible] nesin Type Ann

Domino [illegible] ly Acting Muscle

Lewis T [illegible] Visceromotor Re

Schlesing [illegible] Tone, Ann New

Schlesinger E B, Drew, A L, and Wood B (R N) Clinical Studies in the Use of Myanesin Am J Med 4 365 1948

Schlesinger, E B, and Ragan C Muscle Spasm in Acute Low Back Pain and Similar Syndromes Am J Med 1 621 1946

Schlesinger, E B and Stinchfield, F E The Use of Muscle Relaxants as an Aid in the Diagnosis and Therapy of Acute Low Back Disorders, J Bone & Joint Surg 33 480, 1951

Weiss A A, D Oronzio, G B and Ebel A Evaluation of the Effect of Zoxazolamine (Flexin) on Spasticity, J Urol 78 294 1957

Wolff H G Some Observations on Pain, The Harvey Lectures Series XXXIX 39 95 1943 1944

Direct trauma to muscle
Protective splinting in the low back and cervical spine syndromes
Orthopedic deformities with reflex spasm
Acute and subacute arthritic states with secondary muscle splinting
So called myositis
The potentiation of traction effect as in acute stiff neck, low back syndrome, etc
As a therapeutic test to demonstrate the part played by nerve root compression in perpetuating muscular splinting as in herniated nucleus pulposus cervical and lumbar

Spasticity
To improve the efficiency of performance by reducing hypertonicity
To permit range of motion exercises and retraining
To prevent the appearance of irreversible contractures

Miscellaneous uses
In evaluating the reversibility of contractures
In allowing gynecologic, urologic, and dental examinations of the severely spastic patient
In the management of crises of tetanus athetosis and rabies
As adjuvants to anesthesia (As this is a field for special consideration it will not be elaborated upon here)

ROUTES OF ADMINISTRATION

To achieve predictable and reasonably effective responses available muscle relaxant drugs must be given by the intravenous or intramuscular routes

Intravenous—The most useful compound for intravenous use is the 2 per cent supersaturated solution of mephenesin It is a potent pharmacologic agent with established toxic side effects These are predictable and avoidable when the drug is used under reasonable circumstances

Intramuscular—Although curare is an effective drug by the intravenous route it is not a practical agent for use in ambulatory patients or, indeed, in any patients who are not under ideal operating room conditions Various intramuscular preparations including the emulsions with the advantage of slowed release have a real but narrowly limited usefulness Their value lies in the treatment of muscle spasm of the acute type such as in the low back syndrome Curare has histaminic effects which can prove dangerous to patients bordering on shock It can be mentioned here parenthetically that curare is an excellent drug for the treatment of dysmenorrhea Whether this is due to its effect on the spiral muscles of the uterus or to some complex pharmacologic *effect unrelated to its usual* pharmacologic effect I am not in a position to say

Oral—The earliest preparation in wide use was mephenesin, followed by meprobamate (Equanil Miltown) zoxazolamine (Flexin), and many others [These include carisoprodol (Soma) ethopropazine (Parsidol), methocarbamol (Robaxin) orphenadrine (Disipal) procyclidine (Kemadrin), and promoxolane (Dimethylane) among others Ed] Although all of these are not generically related they share the fact of minimal effectiveness by oral administration Drugs

Several of these types of vertigo are of particular interest in connection with the use of drugs Vertigo may occur in the aura of epilepsy or in migraine One of the causes of vertigo due to brain stem lesions is the administration of streptomycin Aural vertigo may be caused by wax in the external ear, blockage of the Eustachian canal and sudden changes in atmospheric pressure, acute and chronic suppurative otitis media, drugs, including quinine and salicylates herpes zoster of the geniculate ganglion, acute nonsuppurative labyrinthitis, recurrent aural vertigo (Ménière s syndrome), and motion sickness

CLINICAL APPLICATIONS

Recurrent Aural Vertigo (Meniere's Syndrome, Endolymphatic Hydrops) — Meniere s syndrome comprises three principal symptoms vertigo, tinnitus, and deafness Hydrops of the labyrinth first was observed by Hallpike and Cairns in a dock laborer who met death accidentally during an attack of Meniere s syndrome Their examination and those of later observers in other patients revealed a marked hydropic swelling of the utricle and the saccule with herniations into the horizontal semicircular canal

Recurrent aural vertigo probably is of varied etiology Characteristically there is recurrence of the attacks of severe giddiness leading to vomiting and prostration and usually associated with tinnitus and increasing deafness The disorder runs a protracted course with a tendency to disappearance of the vertigo as the deafness increases

Several suggestions have been made concerning the cause of the labyrinthine edema One hypothesis is that it is the result of a chronic progressive herpetic neuritis of the vestibular labyrinth, being due to the rupture of one or more vesicles, with the release of a toxic fluid The size and number of vesicles rupturing at one time determine the severity of the attacks According to this hypothesis the paroxysmal nature of the disease is due to the continued formation and periodic rupture of these vesicles However, the similar appearances in the canals of many labyrinths from those over the age of 40 who have had no symptoms of Ménière s disease, together with the absence of pathologic changes in the neurones do not favor this ingenious hypothesis

Another suggestion is that physical or emotional stimuli produce injury to certain cells in capillary loops which owing to the local anoxia produced are injured, with release of histamine This is followed by alteration of the permeability of cell membranes of the capillary wall, transudation of fluid, and changes in distribution of electrolytes

Some have held an allergy responsible for the attacks ascribing to certain patients with Ménière s disease an action of histamine in dilating capillaries and in altering their permeability, thus provoking endolymphatic changes The low incidence of any allergic symptoms such as hay fever, rhinorrhea asthma eczema or colitis in such patients is not in favor of this etiology

The attack of vertigo may be an indication of disturbances in water metabolism and capillary function During attacks increase in weight and other evidence of water retention may be observed It has been suggested that the tissues responsible for Méniere's syndrome were sensitized or had increased avidity for sodium

THE CHOICE OF AN AGENT FOR DISTURBANCES IN EQUILIBRIUM

Paul K Smith, Ph D

INTRODUCTION

It was postulated early that, since interference with the labyrinth causes dizziness, the normal function of the labyrinth is to control equilibrium.

Impulses which aid in maintaining the body in an appropriate position in space include those from the otoliths which are concerned mainly in the orientation of the body with respect to gravity and those impulses from the semicircular canals which respond to movement and to angular momentum. Important contributory roles are played by visual impulses, impulses from the proprioceptors of the ocular muscles, and impulses from the proprioceptors of the joints and muscles of the neck which convey information relating the position of the head to that of the rest of the body, and impulses from the lower limbs and trunk. These afferent impulses are related mutually by central mechanisms, of which the cerebellum, the vestibular nuclei, the posterior longitudinal bundle, and the red nuclei probably are the most important.

Vertigo is the result of certain types of disturbance of the nervous mechanism involved in the maintenance of normal body balance. It may be defined as the consciousness of disordered orientation of the body in space. The external world may appear to move, the body itself may be felt to be moving or the positions and movements of the limbs may seem to be ill-adjusted and unsteady. Vertigo may be accompanied by forced movements of the body, such as falling, by nystagmus and sometimes diplopia, by the phenomenon of past pointing, and by such visceral disturbances as pallor, sweating, alterations in the pulse rate and blood pressure, nausea, vomiting, and diarrhea. Impulses from these lower centers reach the cerebral cortex mainly in the temporal and parietal lobes and so influence voluntary movements.

Dizziness or vertigo may result from stimulation, irritation, or disease of the sensory end organs of the afferent path, or of the central mechanisms concerned. It may be caused by psychogenic factors, cortical disturbances, impulses of ocular or of cerebellar origin brain stem lesions lesions of the eighth nerve, or by labyrinthine impulses.

believed that gastric distention occurs from loss of gastric tone, followed by generalized contraction of the duodenum and abdominal musculature

A precise estimate of the incidence of motion sickness in man is obviously impossible, for it will vary with the type, severity and duration of motion The incidence of seasickness ranges from 0 8 per cent on large ocean liners to almost 100 per cent in certain combat landing operations It is estimated that 40 per cent of any population group are susceptible to seasickness on sudden exposure to rough weather at sea The incidence of airsickness shows a similar variation depending upon the persons tested, intensity of turbulence, type of plane, and duration of flight No reliable data are available on the incidence of car sickness, train sickness or sickness on various other conveyances

It is common knowledge that some individuals may be prostrated by turbulence which is completely without effect upon their neighbors It can be stated categorically that for any specific case the susceptible person cannot be differentiated from the resistant except by exposure to the motion in question The susceptibility of children to motion is high and it decreases steadily with age It is not known whether this is due to anatomic or physiologic changes or to gradual adaptation to motion

The relationship between vestibular stimulation and motion sickness is well established Animals with eighth nerve section or with bilateral labyrinthectomy are no longer susceptible to motion The receptors in the labyrinth consist of the cristae of the semicircular canals which respond primarily to angular acceleration and sensory epithelia or maculae of the otolith organs sensitive to linear acceleration The failure to observe nystagmus during seasickness is evidence that the stimulation of the semicircular canals during rolling and pitching is inadequate to account for the development of seasickness There is incontrovertible evidence that motion sickness may be produced on elevators and other devices giving only linear acceleration

The sites have been more specifically identified as the utricular maculae since the saccule has been absolved from participation in labyrinthine static or kinetic reflexes Simple up and down movements which could only act upon the otoliths effectively produce motion sickness Further, in contrast to angular acceleration the magnitude of linear accelerations developed during pitching and heaving and even in rolling is many times the receptor organ threshold

Perhaps the most convincing demonstration of the importance of utricular stimulation in producing motion sickness is the effect of head positioning The relief obtained by a motion sick individual upon reclining constitutes the oldest and best treatment discovered for this ailment Although various explanations have been offered to explain this relief, it now seems probable that the underlying mechanism is the shifting of the utricular maculae to less vulnerable positions

The main pathway of impulses originating in the labyrinth proceeds by way of the eighth nerve to the vestibular nucleus then traverses the vestibular portion of the cerebellum (probably nodulus and uvula), stimulating the chemosensitive trigger zone in the medulla, and, finally, reaches the emetic center itself

There can be little doubt that the labyrinthine stimulation is by far the most important factor in the genesis of any form of motion sickness Other factors, including psychologic ones, must be placed in decidedly subordinate cate

The usual history is that the patient has suffered from slowly progressive deafness and tinnitus in one or both ears for months or even years and then suddenly has an attack of giddiness In a severe case the patient is literally prostrated, vomiting develops, and there may be diarrhea The pulse may be rapid or slow and the blood pressure raised or lowered and there may be profuse sweating Double vision may occur and in very severe cases consciousness may be lost On attempting to stand and walk, the patient is unsteady and staggers The vertigo may last from half an hour to many hours and then gradually subside

The attacks tend to occur at irregular intervals and with varying severity The tendency is for the attacks to diminish in severity spontaneously and finally to cease, with an increase of the deafness

Vertigo Without Deafness—The majority of cases of vertigo are not associated with auditory symptoms or with other signs of disease of the central nervous system Many of these usually are classed under the heading, pseudo-Meniere's syndrome Some cases of atypical Meniere's syndrome are really only early cases of true Meniere's syndrome before the development of the classical symptom triad

The pathologic disturbances which are associated with most clinical conditions giving origin to pseudo-Meniere's syndrome are not known The postural vertigo which is characteristic of this group usually corresponds to the type which is most frequent in proved disease of the posterior fossa in that a positional nystagmus occurs which changes direction with alteration of the position of the head *A central origin is therefore suggested*

Vestibular neuronitis is a condition in which patients suffer a sudden loss of vestibular function, as a rule on one side only but without any impairment of hearing It is believed that the lesion lies somewhere in the vestibular neurones, and it may be associated with an infection, although in many cases there is no obvious causal factor This also may be the condition known as epidemic labyrinthitis

Vertigo may be a symptom of some toxic disorder Its occurrence in septic patients and after the administration of certain drugs, especially streptomycin, is evidence for this assumption

Occasionally vertigo is a symptom of hypertensive disease Central causes include epilepsy, disseminated sclerosis certain temporal lobe tumors some tumors of the cerebellopontine angle or in the midline where the vestibular connections in the cerebellum are involved, and thrombosis of the posterior inferior cerebellar artery Usually these are associated conspicuously with other clinical signs of intracranial disease

Motion Sickness—Centuries before the Christian era, motion sickness was well known as evidenced by allusions in the writings of Homer and Hippocrates

The usual symptoms of motion sickness include anorexia, drowsiness, pallor, epigastric awareness, malaise, cold sweat, nausea, vomiting, and retching Salivation headache, increased intestinal peristalsis, fatigue, and mental depression also may occur The sequence, number and intensity of symptoms may vary considerably depending upon the individual and the kind and severity of motion experienced

The once prevalent concept of pylorospasm and reversed peristalsis of stomach and esophagus largely has been abandoned On the contrary, now it is

gery, nausea and vomiting after temporal bone surgery, acute vertigo from labyrinthine hydrops, and vertigo due to suppurative labyrinthitis Dimenhydrinate (Dramamine), administered in the form of tablets or rectal suppositories has been reported to be helpful in patients after the fenestration operation

In studies on human subjects it has been demonstrated that cyclizine (*Marezine*) uniformly depressed the labyrinth and prolonged the onset and shortened the duration of nystagmus Meclizine (Bonamine) also prolonged the onset of nystagmus but its effect was not as great or predictable as that of cyclizine Promethazine (Phenergan) also has been mentioned as a useful drug for the treatment of recurrent aural vertigo

Dimenhydrinate was the first antihistamine to be used for the prophylaxis of seasickness and its effectiveness has been rapidly and repeatedly confirmed The observation that dimenhydrinate and diphenhydramine were effective raised the interesting possibility that antimotion sickness efficacy might be related to antihistamine potency This hypothesis was rapidly disproved by the demonstration that many strong antihistamines afford no protection against motion sickness Thus no correlation appears to exist between antihistamine potency and motion sickness protection

Antihistamines which have recently attracted considerable interest are members of the piperazine series The hydrochlorides of cyclizine (Marezine) and meclizine (Bonamine postafene) have been shown to be effective against both sea and airsickness The most striking feature of the effect of Bonamine has been the long duration of action Given 24 hours prior to take off, Bonamine has protected soldiers and airmen against airsickness Given once daily it will protect against seasickness Recent work suggests that its duration of action may be even longer, since a single 50 mg dose taken before sailing afforded protection comparable to that obtained with other medications given 3 times daily for the first 2 to 3 days of the crossing

Vitamins —The ever expanding areas of vitamin therapy coupled with the empiric search for methods of treatment of vertigo made it almost inevitable that vitamins be tested for effectiveness It has even been suggested that Menière s syndrome is due to a deficiency of niacin or riboflavin or both

Nicotinic acid in large doses sometimes is reported to be effective, perhaps by improving the blood supply In several hundred patients treated with large doses of nicotinic acid one investigator was able to secure complete remission of the symptoms in two thirds of the patients as long as they continued on the treatment After cessation of treatment, symptoms returned in a few days to 6 months Goodman, in a smaller number of patients observed no particular improvement with nicotinic acid Others have used pyridoxine riboflavin and thiamine and reported some success

The widespread use of pyridoxine in the therapy of nausea and vomiting in pregnancy and irradiation sickness stimulated its trial in motion sickness Recently a report of a study appeared in which 500 seasick patients received 50 mg pyridoxine by mouth with marked improvement in a third of the patients Attempts to confirm this observation in a controlled study of seasickness prophylaxis was unsuccessful

gories These latter factors may aggravate an already existing illness or, in isolated instances, may even constitute the primary causes of motion sickness

GENERAL PHARMACOLOGIC CONSIDERATIONS

Vertigo Other Than Motion Sickness—The existing numerous methods of treatment in vertigo, if they produce symptomatic relief, do so in spite of the lack of any basic understanding of the pathology involved Medical treatment of endolymphatic hydrops usually has been based either on the hypothesis that permeability of the capillaries of portions of the labyrinth was increased or on the hypothesis that fluid or electrolyte metabolism was disturbed

On the assumption that the labyrinthine cells have an increased affinity for sodium which results in retention of the sodium ion and the production of the hydrops of the endolymph and perilymph of the labyrinth it has been proposed to reduce the intake of sodium and ensure its maximum elimination by giving acid forming diuretics

Some workers suggest than an increased concentration of serum sodium observed in some cases of Meniere s disease indicates loss of tissue potassium, just as a high level of serum calcium accompanies loss of calcium from the tissues For this reason it has been suggested that the depleted potassium in tissues can be restored and electrolyte equilibrium re established by administration of additional potassium

On the basis of the theory that the vertigo is caused by an action of histamine in providing a vascular disorder of the small vessels of the labyrinth resulting in excessive formation of endolymph, desensitization to histamine has been proposed In those patients responding with an excessively large wheal and flare to 0 01 mg of histamine given intradermally, gradually increasing doses of histamine have been reported to provide relief of the symptoms presumably on the basis of desensitization Histamine desensitization, as a method of treatment, has generally lost favor

It has been suggested that in Meniere s syndrome there is an arteriolar spasm of end arteries in the membranous labyrinth which results in a passive dilation of the capillary venule network distal to the spasm In the distended loop there may be sludging of blood, liberation of toxic metabolites, hypoxia of vessel walls and increased capillary permeability leading to tissue edema and increased accumulation of endolymph Depending on which vessel or vessels are involved, the patient may experience primarily vertigo, hearing loss, tinnitus or a combination of these For these reasons vasodilating agents such as nicotinic acid have been used Actually it appears that nicotinic acid was recommended in treatment of endolymphatic hydrops because a large percentage of pellagrins have rotational vertigo

Motion Sickness—There is no ailment other than motion sickness, with the possible exception of the common cold, or hiccups for which the general populace and the medical profession alike have prescribed with greater assurance and originality The treatments are generally uncontrolled frequently amusing and occasionally ingenious The recommendations range from cuffs about the neck for control of cerebral blood flow to corsets for abdominal support, from gastronomic heroics to Spartan self restraint from ingestion of herbs to injections of vitamins

Attempts to correlate the ability of a drug to combat motion sickness with its

Autonomic Drugs —Epinephrine in doses of 0 3 to 0 6 ml. of the 1 1,000 solution given intravenously slowly has been used for the therapy of acute attacks of vertigo

The mixture of dihydrogenated ergot alkaloids known as Hydergine has been used in the therapy of vertigo Patients are given one of the 0 5 mg sublingual *tablets* every 4 hours

On the assumption that acute attacks of vertigo are associated with cholinergic hyperactivity, *atropine has been given subcutaneously in doses of 0 5 to 0 75 mg* Relief of the symptoms is said to occur in 15 to 30 minutes

There is evidence that several *parasympatholytic drugs are effective in motion sickness* Atropine and l hyoscyamine in doses of 1 mg are effective but perhaps because it produces milder side effects, hyoscine (scopolamine) is the most widely used of these drugs although continued administration may produce blurring of the vision and even more serious side effects Hyoscine in initial doses of 0 5 to 1 mg is effective in airsickness especially Its use in seasickness is less desirable since the repeated doses that often are required may lead to unpleasant symptoms

Antiallergic Therapy —Presumably on the assumption that the release of histamine is responsible for the local edema of the labyrinth in many patients with *vertigo therapy has been directed toward desensitizing the patient to histamine or* toward blocking the effects of histamine Often patients first are tested for histamine sensitivity by intracutaneous injection of 0 05 ml of a 1 10 000 solution of histamine base Positive reactors in 5 minutes develop a bleb 0 75 to 1 inch in diameter with an erythematous area 2 to 3 inches across This reaction is still visible after 20 minutes Attempts are then made to desensitize patients reacting to histamine by giving them 2 to 3 mg of histamine phosphate intravenously slowly in 250 ml isotonic sodium chloride solution The rate usually must be maintained at 15 to 60 drops per minute to avoid headache Food or antacids are given to *protect the patient from the oversecretion of hydrochloric acid This dose of* histamine is repeated daily until relief of symptoms occurs

Others advocate the much more gradual desensitization to histamine, beginning with 0 05 ml of a 1 10 000 solution subcutaneously, then giving the drug on alternate days increasing the dose each time by 50 per cent up to a dose of 0 4 ml of a 1 1 000 solution

The antihistaminic drugs diphenhydramine (Benadryl), cyclizine (Marezine) and meclizine (Bonamine) all in doses of *50 mg* dimenhydrinate *(Dramamine)* in doses of *100 mg* and promethazine *(Phenergan) in doses of 12 5 mg may be used in the therapy of vertigo Because of its* long duration of action meclizine usually is given only once a day but the others may be given 3 times a day

The most consistently effective therapy of all forms of motion sickness is one of several antihistaminic drugs Cyclizine 50 mg meclizine 50 mg, and promethazine 25 mg, are the most effective agents against all types of motion Bonamine is preferred by some since one dose a day may be sufficient *while the* others may be required 3 times a day Dimenhydrinate (Dramamine) 100 mg and diphenhydramine *(Benadryl), 50 mg also are* effective when given 3 times a day

Sedation —Acute attacks of vertigo may be treated with sodium phenobarbital in 0 1 Gm doses given parenterally or secobarbital sodium in 0 2 Gm doses given

Dehydrating Agents—Restriction of the intake of sodium in the diet has proved to be of value in those cases in which retention of fluid is a major factor. The use of a powerful diuretic is indicated if there is evidence of fluid retention. Recently two investigators have reported good results after the administration of acetazolamide (Diamox). In 6 patients with Meniere's disease the dizziness disappeared and sometimes the hearing improved. A salt free diet combined with a restriction of fluid intake may be helpful. Ammonium chloride and other acidifying salts may be effective. Others have used a diet with normal sodium content but proportionally higher in potassium. To achieve this, from 6 to 10 Gm of potassium chloride in aqueous solution were given daily. Talbott and Brown treated 40 patients with this regimen and reported that all had been relieved but none cured. Most patients experienced an exacerbation of symptoms within a few days after discontinuing treatment with potassium chloride.

The introduction of ion exchange resins into therapy has provided another means of controlling body water and electrolytes. The potassium and ammonium form of a cross linked polyacrylic (carboxylic) cation exchange resin has been used.

Miscellaneous—The vestibulotoxic properties of streptomycin have been used in Meniere's disease to abolish vestibular function. Unfortunately vestibular function on both sides is affected by the drug and, if function is lost in both, in older patients it may well result in a greater incapacity than the disease for which it is given.

If, after several months, the patient shows no response to medical measures and especially if the vertigo incapacitates him from following his occupation, surgical treatment may be considered. The surgery requires the injection of alcohol into the internal ear or intracranial division of the vestibular fibers of the eighth nerve. Cawthorne reported the effects of labyrinthotomy followed by opening the endolymphatic space in 48 cases of endolymphatic hydrops. Relief of vertigo was secured in all of these cases.

Section of the vestibular portion of the acoustic nerve has the advantage that the hearing may be spared, but it is an intracranial operation which is not without risk.

A DESIGN FOR THE USE OF DRUGS FOR DISTURBANCES OF EQUILIBRIUM

Treatment of vertigo other than motion sickness may be considered under the headings of [illegible] ures to relieve [illegible] the labyrinth, [illegible] uniformly successful. The condition is characterized by spontaneous remissions and one should be very careful not to give credit to therapy when relief from distress may be due to a remission.

With existing therapy the incidence of motion sickness probably can be reduced to one third or less its usual frequency and severity. General measures consist in avoiding irritating foods, alcoholic beverages and unpleasant odors just prior to exposure to motion. Lying supine or with the head tilted back is especially helpful

about its etiology, but because the candidate therapies, necessarily chosen empirically, in many cases have been evaluated carefully with proper attention to controls and comparison with known remedies

Admittedly it will be difficult to study the treatment of vertigo in this manner, but until this is done, perhaps in a cooperative study, the choice of therapy cannot be on a scientific basis

To this point the various drugs have been discussed primarily from the point of view of their effectiveness As with any other drug, however, the practical value is not determined by its effectiveness alone The incidence and severity of side effects are equally important factors Under some circumstances it may be vital that the drug not impair the person's ability to perform his task

In large doses, hyoscine and other belladonna alkaloids have undesirable side effects The peripheral effects include decreased sweating and salivary flow, cycloplegia and cardiac acceleration Centrally, large doses may produce disorientation, excitement, and even hallucinations, giving way to a secondary depression Single doses of hyoscine required to produce such central changes would rarely be given except by accident

Histamine, even in small doses may produce serious hypotension, severe headache, bronchiolar constriction, and gastric hypersecretion

By far the most common side effect of the antihistamines has been sedation In fact, some of them have been shown to compare favorably with clinically employed doses of barbiturates in causing drowsiness There is some evidence that cyclizine and meclizine exert relatively little sedative action Apart from sedation, the most common complaints related to the use of the antihistamine series are symptoms associated with anticholinergic activity dry mouth, blurred vision, dizziness fatigue Since the protection against motion sickness may depend upon the parasympatholytic activity *of the compound, these side effects may be inevitable* in any effective preparation

SELECTED REFERENCES

[illegible] New York 1958 Grune & Stratton
[illegible] holinesterase Activities in the Intracarotid Injection 1954
[illegible] Rhin & Laryng 65 351 1956
DeWeese D D Benadryl in the *Control of Vertigo Preliminary* Report on Its Clinical [illegible] 61 245 1954
Gay, L [illegible] Vestibular Disturbances With Dimen[illegible]
Goodman [illegible] d Treatment a Survey of 268 Cases
Gutner, [illegible] of Meclizine Hydrochloride (Bonamine) *th Notes on Its Value in Comparison* [illegible] M A Arch Otolaryng 62 497, 1955

rectally Phenobarbital, in oral doses up to 0 2 Gm per day is the basic drug used by many to alleviate the symptoms of vertigo

Sedative and hypnotic drugs are known to be effective in motion sickness only in so far as the patient may assume a supine position, thus reducing appreciably the stimulus to the vestibular apparatus

Vitamins —Although there seems to be little evidence that the vertigo of Menière's disease is associated with a vitamin deficiency niacin, riboflavin, and thiamine have been used Nicotinic acid (niacin) is used in doses of 0 1 Gm orally 3 times a day There seems to be no justification for the parenteral administration of the drug as sometimes advocated unless vomiting is persistent Riboflavin and thiamine in 5 mg doses daily have been used Perhaps because niacin is an active vasodilator papaverine in doses of 0 3 to 1 2 Gm also has been used

Dehydrating Agents —On the assumption that the local edema in the labyrinth may be relieved by systemic drugs the principal measures in use are restriction of sodium intake and administration of ammonium chloride and potassium salts The diuretic acetazolamide Diamox) frequently is used in doses of 0 25 Gm per day to hasten sodium excretion

Usually a combination of two of these measures has been used Patients are placed on a diet containing no more than 1 to 2 Gm of sodium per day and are given in addition 6 to 10 Gm of either potassium chloride or ammonium chloride per day In some cases this treatment is continued indefinitely and in others it is used for a few days followed by a few days of rest and observation before therapy is resumed

Miscellaneous —The present unsatisfactory state of the treatment of vertigo with any single drug is well exemplified by the treatment recommended by Kane and Strong They suggest 0 8 mg of atropine sulfate or 0 6 mg of hyoscine hydrobromide subcutaneously plus 0 6 ml of 1 1 000 epinephrine hydrochloride intravenously or 0 1 Gm of ephedrine sulfate orally plus 25 mg of chlorpromazine (Thorazine) intramuscularly plus 25 to 50 mg of pyridoxine hydrochloride intravenously plus 50 mg of dimenhydrinate Dramamine) intramuscularly or subcutaneously

RATIONAL BASIS FOR NEW DRUGS FOR DISTURBANCES IN EQUILIBRIUM

The manner in which drugs exert their protective action in abolishing vertigo and the symptoms of motion sickness remains unknown Until greater insight into the genesis of the disturbances is gained new therapy must be sought on a trial and error basis

Reports on the therapy of Meniere s disease and disturbances of equilibrium other than motion sickness seem to be characterized by a lack of adequate control observations In a disease in which spontaneous remissions are frequent it has been common to associate relief of symptoms with whatever drug was given previously This inevitably has led to confusion uncertainty and the perpetuation of remedies of doubtful value

In contrast to the therapy of other diseases of equilibrium advances have been made in the treatment of motion sickness, not because so much more is known

THE CHOICE OF AN ANTIEMETIC AGENT

John H Moyer, M D, and

William L Wilson, M D

INTRODUCTION

Usually, nausea and vomiting serve no useful purpose, and alleviation of these symptoms may become the primary concern of the therapist Treatment may be quite difficult because so many factors contribute to the development of this symptom complex which is a prominent manifestation of numerous organic as well as psychiatric diseases Obviously, it is preferable to relieve the cause when it is known and is amenable to therapy Unfortunately it may be impossible to determine the etiology and, when known, to eliminate it In such instances symptomatic therapy may be indicated Recently, numerous drugs have been developed which block emesis of various etiologies through depression of specific areas in the brain The sites of action of different antiemetic agents differ and consequently their effectiveness depending on the cause of the vomiting It is the purpose of this communication to review the effective antiemetic agents and to attempt to outline their specific indications in the therapy of nausea and vomiting due to numerous causes

PHARMACOLOGIC CONSIDERATIONS

The Mechanism of Vomiting—Giannuzzi first suggested the possibility of a vomiting center nearly 100 years ago However, it was not until 1948 that Borison and Wang first found that the area most responsive to electrical stimulation was the lateral reticular formation (Fig 7) This area is localized in the midst of other medullary structures that participate in the vomiting act the area controlling salivation, the spasmodic respiratory center, the inspiratory and expiratory center, the vasomotor center, the vestibular nuclei and the bulboexcitatory and inhibitory systems

Like other brain stem structures, the vomiting center is activated by tonic excitatory and inhibitory nervous and metabolic stimuli The center does not initiate vomiting by itself but coordinates the activities of the other neural struc

Hallpike, C S, and Cairns, H Observations on the Pathology of Ménière's Syndrome, Proc Roy Soc Med 31 1317, 1938
Henderson, J A New Type of Treatment of Menieres Syndrome, A M A Arch Otolaryng 59 349 1954
Hoople, G D Symposium Menière's Disease—Medical Treatment, Tr Am Acad Ophth 60 182, 1956
Kane C A and Strong M S Dizziness and Vertigo Diagnosis and Treatment, M Clin [illegible]
Talb[illegible] istituents of the Blood [illegible] 1940
Varg[illegible] Laryng & Otol 72
Walsh, R E The Diagnosis and Treatment of Menière's Disease A M A Arch Otolaryng 64 118 1956
Williams, G D Symposium Medical Treatment of Menière's Disease, A M A Arch Otolaryng 62 573 1955

meclizine (Bonamine) and cyclizine (Marezine), effective antiemetic agents long duration of action and minimum side effects French investigators e menting concurrently with the phenothiazine derivatives, chlorpromazine (T zine) and promethazine (Phenergan), found the former to have a powerful emetic action in animals Additional phenothiazine derivatives such as proc perazine (Compazine) have since been synthesized

The specific pharmacologic actions of antiemetic drugs are imperfectly derstood and much experimental work has been directed toward finding th of action of these agents There seems to be no correlation between antihista and antiemetic potencies For example, Thorazine, a relatively weak an taminic drug, appears to be one of the most potent agents in controlling forms of vomiting whereas many antihistaminic agents apparently exer antiemetic action A central anticholinergic or parasympatholytic action common property of most antiemetic agents Even though Benadryl, Dramar Bonamine and Marezine seem to decrease vestibular sensitivity, their import in this respect relative to antiemetic activity is not clearly understood

The Specific Antiemetic Drugs —

DIPHENHYDRAMINE —Benadryl (diphenhydramine) not only possesses emetic activity but it is an effective antihistaminic agent as well The pharm logic properties are well known About 50 per cent of the patients taking this experience sedation and somnolence Otherwise, side reactions are not marke

DIMENHYDRINATE —Dramamine (dimenhydrinate) is a combination of dipl hydramine and 8 chlorotheophylline The latter contributes little if anythin its action as an antiemetic or an antihistaminic agent Benadryl is equally as ef tive as Dramamine

MECLIZINE.—Bonamine (meclizine) is a weak synthetic antihistaminic ag but both its antihistaminic and antiemetic actions are prolonged It has some a cholinergic properties The incidence of side effects is very low and this agent hibits less sedation and somnolence within therapeutic ranges than any of the ef tive antiemetic agents It may effect its antiemetic properties by depressing b the vomiting center in the medulla and the labyrinthine mechanisms Bonadox merely a combination containing 50 mg of pyridoxine and 25 mg of Bonamine each tablet It is doubtful that the pyridoxine adds much to either the therape effectiveness or the antiemetic potency of the Bonamine when used in this co bination

CYCLIZINE —Marezine (cyclizine) is a water soluble antiemetic agent wh also exhibits moderately potent antihistaminic properties It does not prod adrenergic blockade but is mildly antihypertensive It possesses smooth muscle ar spasmodic properties and blocks the effect of vagus nerve stimulation T duration of action of Marezine is not as long as that of Bonamine being 6 to hours The incidence of sedation and somnolence is quite high We have served several patients in whom somnolence was pronounced for periods up 36 hours

PROMETHAZINE —Phenergan (promethazine) is known primarily for its an histaminic action It has low toxicity, and side effects other than drowsiness a rare Phenergan has very little hypotensive effect and when given parenterally m

tures nearby to produce a patterned response This response is activated through several different pathways For example, the chemoreceptor trigger zone in the floor of the fourth ventricle responds only to emetic chemicals and is connected to the vomiting center through internuncial neurons. Thus, apomorphine does not stimulate the vomiting center directly, but rather indirectly via the chemoreceptor trigger zone The vomiting center is also activated by labyrinthine reflexes and visceral reflexes (Fig 7)

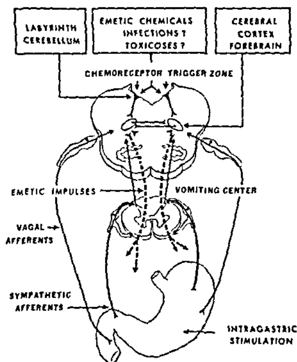


Fig 7—Diagrammatic representation of the mode of action of emetic agents These ... imulation of the ... P H Conner ... ward F, editor ... W B Saunders Co)

Hess also demonstrated emetic responses following stimulation of the di encephalon and other forebrain structures It would seem that unknown afferent supramedullary receptors and pathways not only initiate vomiting but probably influence the reflex excitability of the vomiting center by directing continuous volleys of impulses against it It is quite likely that psychic influences affect vomiting in this manner

Antiemetic Agents—In 1946 diphenhydramine (Benadryl) was found to have antiemetic action An analogue, dimenhydrinate (Dramamine), was reported to be especially effective in motion sickness Further chemical synthesis yielded

hours after the drug is discontinued I have also observed 2 patients who devel oped a peculiar spastic and painful contraction of the trapezius muscle apparentl due to extrapyramidal involvement This too was relieved within 12 hours afte the drug was discontinued

PERPHENAZINE —Trilafon (perphenazine) is also a phenothiazine derivative It is approximately 6 times as potent as chlorpromazine as an antiemetic The incidence of side reactions is somewhat similar to that seen with prochlorperazine Here again the most frequently seen side effect is somnolence Other side effect noted are dryness of mouth nervousness, tremor, and urticaria The side effect other than somnolence are infrequent with doses of 16 mg or less per day but do start appearing in increasing frequency above this dosage There has been no evidence of hepatic toxicity to date and there is less hypotension than observed with other phenothiazine derivatives

It has been used in anxiety states and vomiting and has proved to be an effective agent in both areas As an antiemetic the recommended dose is 4 mg every 6 hours by mouth or 5 mg intramuscularly for parenteral administration Larger doses may be necessary in more severe nausea and vomiting but in those requiring 24 mg per day there may be a marked increase in side reactions the most common being that of somnolence Scurr and Robbie have used it for post operative vomiting in a 5 mg parenteral dose with a two thirds reduction in post operative vomiting as compared to controls with no medication The only side reaction noted was that there was a slight prolongation of the reaction time in these patients

In a fairly large number of cases of nausea and vomiting reported by Weiss and co-workers due to a variety of causes it appears that the agent may give good or excellent results in 80 to 90 per cent of the cases

TRIFLUPROMAZINE —Vesprin (triflupromazine) is another recently developed phenothiazine derivative It is quite effective as an antiemetic and rarely causes hypotension It is approximately 5 times as potent as chlorpromazine It is effective as a dose of 5 mg, 3 times a day, or every 6 hours Large doses should be avoided because of rather severe extrapyramidal signs that may develop how ever these are reversible when the drug is discontinued The other side effects associated with phenothiazine derivatives appear to be less frequent with triflu promazine

Phenothiazine Derivatives (General Comments) —At this time it is apparent that phenothiazine derivatives as a group have antiemetic activity Most of the published reports concern chlorpromazine and compare it with non phenothiazine antiemetics Reports are appearing in the literature concerning other phenothia zine derivatives, but to date they lack the completeness of the information available on chlorpromazine Because of this fact most of the information discussed in this chapter refers to chlorpromazine It is not the intention of the authors to intimate that chlorpromazine is the most effective or most desirable of the phenothiazines From the reports that have appeared concerning the use of perphenazine prochlorperazine and triflupromazine it would appear that these agents are also quite effective antiemetics and are approximately 5 to 6 times more potent than chlor promazine These three derivatives also produce less adrenogenic blockage and

actually cause an increase in blood pressure Like Thorazine, Phene... sedative properties and potentiates analgesics and hypnotics

CHLORPROMAZINE —Thorazine (chlorpromazine) like Phenergan... thiazine derivative unlike Phenergan, Thorazine has little if any a... activity but is highly active in its effect on the autonomic nervous syste... acts as an adrenergic blocking agent In addition, the drug affects th... blocking the vomiting reflex and produces sleep from which the patie... aroused It is also used for the treatment of mental and emotional diso... potentiates the action of analgesics and sedatives No doubt there are... other central nervous system effects which have not been uncovered as ye... drug has a bitter taste, and when applied to the mucous membrane it acts as... anesthetic much like cocaine It can be administered both orally and pare... and is apparently well absorbed following the former route of administratio... may increase the pulse rate but acute studies in the laboratory indicate that ca... output is not affected appreciably The electrocardiogram is altered only... very large doses of the drug are administered Although chlorpromazine app... to be a cerebral depressant, cerebral oxygen uptake is not reduced by doses u... clinically

The effectiveness of Thorazine as an antiemetic agent probably depends... part on its competitive affinity for receptors in the chemoreceptor trigger zon... In addition intravenous administration of 6 mg per kilogram of Thorazine in... creases protection against the emetic action of intragastric copper sulfate Since... copper sulfate acts on the medullary vomiting center via the visceral afferents with... out involving the chemoreceptor trigger zone, a second site must be postulated for... Thorazine's activity the reticular vomiting center

For the routine use of Thorazine as an antiemetic agent, a dose of 25 mg or less will minimize the incidence and severity of side effects At lower doses the drug usually loses its effectiveness An initial 10 mg dose is best for the ambula... tory patient If this is ineffective and side reactions are not marked, it can be increased to 25 mg given every 4 to 6 hours

PROCHLORPERAZINE —Compazine (prochlorperazine), like chlorpromazine, is a phenothiazine derivative Laboratory observations suggest that in equivalent doses it is even more potent (5 times) than chlorpromazine as an antiemetic The stability both in the powdered form and in solution is comparable to that of chlor... promazine It produces less adrenergic blockade and consequently less hypotension than chlorpromazine

The dose of Compazine when used for the treatment of nausea and vomiting is 5 mg 4 times daily to start, it then should be adjusted according to patient re... sponse It should probably not exceed 60 mg a day (15 mg per dose) Within this dosage range the only frequent side reaction is that of somnolence, which is observed in 10 to 20 per cent of the patients being treated Jaundice and blood ...yscrasias have not been observed

When doses of more than 60 mg per day are employed, the incidence and ...verity of side effects rise sharply These include somnolence, seen in about two-...rds of the patients and dizziness, hypotension tachycardia and dry mouth ...n in one third to one half of the patients These are all reversible...

A reversible paralysis agitans like syndrome occasionally develops in patients taking extremely high doses of Thorazine (more than 1,000 mg per 24 hours), but this reaction is rare when the drug is used as an antiemetic. Jaundice is seen in a small number of patients. According to Kelsey and his associates the majority of the patients developing jaundice during Thorazine therapy are receiving large doses for psychiatric reasons. The incidence of jaundice following Thorazine is about 1.4 per cent in institutionalized psychiatric patients—almost twice as great as that seen when Thorazine is used as an antiemetic. Although the clinical picture may simulate acute infectious hepatitis, the laboratory findings usually indicate obstructive jaundice. Agranulocytosis may be seen within 7 weeks after the institution of Thorazine. Therefore, serial white cell counts are important in warning of this complication.

[Trimethobenzamide hydrochloride (Tigan), a reputed antiemetic drug which is not a phenothiazine derivative, has been introduced too recently to be able to establish its relative usefulness with assurance. Ed.]

CLINICAL APPLICATIONS

Drug-Induced Emesis.—Nausea and vomiting associated with drug administration is due to increased sensitivity, drug toxicity, or overdosage. Most emetic drugs act by one of the following methods: (1) stimulation of the chemoreceptor trigger zone in the medulla which is followed by secondary stimulation of the vomiting center over the connecting neurons, (2) direct stimulation of the vomiting center, (3) gastrointestinal irritation with reflex stimulation of the vomiting center (Fig. 7). The antiemetic agents, when effective, block off one or more of these causative mechanisms.

Opiates—morphine, meperidine, methadone, and Pantopon—probably elicit vomiting by stimulating the chemoreceptor trigger zone directly. In addition they may act indirectly by increasing vestibular sensitivity, similar to the mechanism of motion sickness with secondary stimulation of the vomiting center; this response is most likely to occur in ambulatory patients. Benadryl, Dramamine, Marezine and Bonamine appear to be more effective than Thorazine in combating opiate-induced nausea and vomiting. *The fact that these antiemetic agents depress vestibular sensitivity may account in part for the fact that they are more effective than Thorazine in alleviating opiate-induced vomiting.*

Table 19. Therapeutic Response to Chlorpromazine of Nausea and Vomiting Due to Drug Administration

Etiology of Nausea and Vomiting	Number of Patients Treated	Therapeutic Response* in Per Cent: Excellent	Improved	Failure
Digitalis	16	75	25	—
Nitrogen mustard	40	60	35	5
Antibiotics	20	60	40	—
Aminophylline	12	67	33	—
Veratrum (protoveratrine)	30	—	33	67
Miscellaneous	9	11	78	11

*Therapeutic response: excellent = complete arrest of nausea and vomiting; improved = vomiting arrested but nausea continued; failure = no improvement of nausea or vomiting.

subsequently less hypotension None of them have been demonstrated to cause jaundice but pherphenazine has been implicated in a case of agranulocytosis However, where the aforementioned side effects are less frequent than seen with chlorpromazine, the incidence of agitation, anxiety, and signs of extrapyramidal irritation appears to be more common This has been reported with perphenazine and prochlorperazine to a limited extent However, the incidence observed with triflupromazine is considerably higher and occurred rather consistently on a dose of 150 mg per day (a comparable dose of chlorpromazine would be 750 mg)

When using triflupromazine or prochlorperazine a dose of 5 mg every 6 hours by mouth appears to be quite effective in preventing vomiting The comparable dose of perphenazine would be 4 mg every 6 hours When vomiting is severe, it would be preferable to start with an intramuscular dose of 5 mg (any of the three preparations) and after the vomiting is controlled to change to the oral route for administration

Further information will have to be obtained before the complete picture of side effects of these newer phenothiazine derivatives can be obtained

[There has been insufficient experience at this time with pipamazine (Mornidine) for a proper relative evaluation Ed]

SIDE EFFECTS OF ANTIEMETIC DRUGS —Sedation, dizziness, dry mouth, weakness, fatigability, blurring of vision, incoordination, and lightheadedness as well as occasional headaches, insomnia, nervousness, constipation, and diarrhea are commonly seen during antiemetic therapy These side effects, although usually mild, occur in 20 to 75 per cent of all patients and the severity is frequently proportional to the dosage The incidence of side effects and the severity of these responses vary a great deal among the various antiemetic agents Since tolerance is unpredictable, the initial dose should be given when the patient is not exposed to industrial or transportation hazards There is no apparent relationship between the cause of vomiting and the development of side reactions Intramuscular administration of antiemetic agents is sometimes followed by pain at the injection site, and phlebitis may occur after intravenous infusion The side reactions associated with oral administration may also appear in intensified form after parenteral therapy

Although bone marrow depression, hepatic dysfunction, and vascular collapse occasionally follow administration of these drugs, these reactions apparently occur most frequently after the use of Thorazine About 12 per cent of the patients treated with Thorazine experience a significant hypotension The maximal effect usually occurs 30 to 40 minutes after intramuscular injection and 60 to 90 minutes following oral administration No consistent changes in cardiac output have been observed and renal hemodynamics remain essentially unchanged even though the blood pressure is reduced The usual hypotensive reaction is mild but depressions of 30 to 40 mm Hg have been reported upon assumption of the upright position Therefore patients receiving Thorazine parenterally should remain supine for 30 to 40 minutes after the maximal hypotensive reaction occurs The blood pressure effect is an initial response and usually is not observed after the third or fourth dose When tachycardia occurs the pulse rate usually increases only 10 to 20 beats per minute

upon frequency of administration, rather than on the massive doses (300 to 600 mg per day) generally used When it is used in this dosage range, hypotensive episodes are likely, especially following parenteral administration

Nausea and Vomiting Associated With Infection and Toxicosis—Thorazine is the most effective agent for treating emesis secondary to infection in adults hepatitis, cholecystitis, acute salpingitis, pneumonia, and urinary tract infections The emetic mechanism of gastroenteritis probably is similar to that of drugs causing vomiting by intestinal irritation About 90 per cent of several groups of patients with acute gastroenteritis obtained an excellent therapeutic response with Thorazine (Table 20)

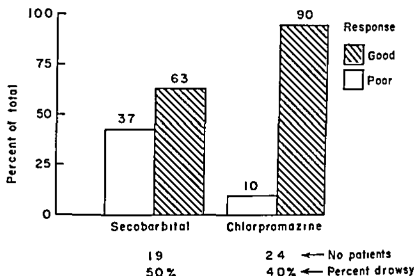


Fig 8—A comparison of the antiemetic effect of chlorpromazine and secobarbital Nausea and vomiting were arrested in 90 per cent of the patients receiving chlorpromazine ... groups ... lf ... tic ... ra peutic effectiveness (Courtesy Dr C W Daeschner from Moyer, John H Effective Anti emetic Agents In Conn, Howard F editor Efficacy of New Drugs M Clin North America March, 1957, Philadelphia, W B Saunders Co)

Daeschner and associates compared Marezine, Bonamine, Thorazine, secobarbital, and placebo in children and found no appreciable difference in the therapeutic response (about 90 per cent) to Thorazine and Marezine, both of which were significantly superior to Bonamine, placebo, and sedation with secobarbital (Fig 8) The antiemetic agents (especially Marezine) were highly successful in controlling the vomiting associated with common pediatric infections and toxicosis Drowsiness, the only common side effect, was less frequent with Bonamine and Marezine compared to that seen with Thorazine and secobarbital Dizziness, tachycardia, and dry mouth occasionally accompanied Thorazine administration

Nausea and vomiting provoked by the various toxicoses in adults—diabetic acidosis, leukemia, hepatic carcinoma, carcinomatosis, and brain tumor—respond

Drug (digitalis, apomorphine, etc.) emesis that results from direct stimulation of the chemoreceptor trigger zone is most effectively blocked by Thorazine (Table 19), which depresses this structure. Thorazine is also the most effective antiemetic agent for treating nausea and vomiting associated with the use of drugs (aminophylline, antibiotics, etc.) which produce vomiting by gastrointestinal irritation. The mechanism of the vomiting commonly seen with nitrogen mustard therapy remains obscure. Thorazine is effective for combating this reaction clinically whether given prophylactically or therapeutically.

The results of using Thorazine in treating the nausea and vomiting associated with veratrum administration in the hypertensive patient vary. As with intragastric copper sulfate, toxic doses of veratrum stimulate the nodose ganglion which propagates emetic impulses over the afferent vagus to the vomiting center without traversing the trigger zone (Fig. 7). Presumably, therefore, in order to be effective against this type of emesis, the antiemetic agent must depress the medullary vomiting center directly. Although Thorazine appears to exert this type of response, in my experience it has little if any beneficial effect on veratrum induced nausea and vomiting (Table 19).

When Thorazine is used for the therapy of drug induced emesis, it is usually necessary to give the first dose parenterally, following which the oral route may be used. Usually 25 mg. given intramuscularly is adequate to arrest vomiting, but, if not, an additional 25 mg. can be given after 1 hour if excessive sedation or hypotension has not occurred. After vomiting has been arrested, Thorazine can be given orally or rectally in a dose of 10 to 50 mg. every 4 to 6 hours depending on the recurrence of nausea and vomiting and their severity. The dose requirement for a given therapeutic response, when the drug is given rectally or orally is usually about twice as large as that necessary by the intramuscular route. Thorazine should rarely be given intravenously since cardiovascular side reactions (particularly hypotension and tachycardia) are much more frequent following this route of administration than by any other route when equal doses are used.

Because of the lower incidence and severity of side effects, Bonamine, Marezine, Benadryl, and Dramamine appear to be more useful in the prevention of nausea and vomiting associated with drug administration. However, if these are ineffective, Thorazine should be tried. When used either prophylactically or therapeutically, Dramamine and Benadryl should be given in doses of 50 to 100 mg. orally. When the patient is actively vomiting, the drug can be given parenterally. When Bonamine or Marezine is used, 25 to 50 mg. of the former, or 50 mg. of the latter, is given. When employed for the prevention of nausea and vomiting associated with antibiotic administration, I prefer a preliminary trial of Bonamine (25 to 50 mg.) or Dramamine (50 to 100 mg.) given orally about 30 minutes before the administration of the antibiotic because of lower incidence of side effects. If these are ineffective, I would then use Thorazine.

Not only does Thorazine control the nausea and vomiting in acute and post alcoholic states but it also relieves the motor excitement and provides beneficial sedation. The antiemetic action allows these patients to tolerate oral feedings earlier so that dehydration and nutritional deficiencies can be corrected more rapidly. The effectiveness of Thorazine in the alcoholic patient seems to depend

upon frequency of administration, rather than on the massive doses (300 to 600 mg per day) generally used When it is used in this dosage range, hypotensive episodes are likely, especially following parenteral administration

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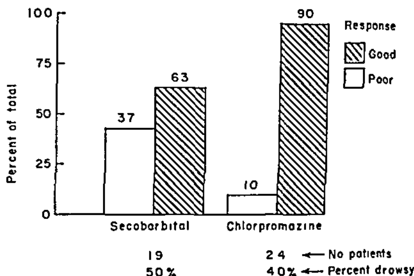


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Table 20 Diagnosis and Clinical Response to Chlorpromazine of Nausea and Vomiting Due to Infections and Toxicoses

Etiology of Nausea and Vomiting	*Number of Patients Treated*	*Therapeutic Response in Per Cent*		
		Excellent	*Improved*	*Failure*
Infection				
Acute gastroenteritis	26	88	4	8
Hepatitis	10	60	40	—
Cholecystitis	3	100	—	—
Acute salpingitis	2	100	—	—
Miscellaneous	4	50	50	—
Toxicosis				
Carcinomatosis	50	78	16	6
Diabetic acidosis	7	100	—	—
Uremia	18	56	33	11
Leukemia	3	100	—	—
Miscellaneous	9	67	33	—

Table 21 Comparison of Therapeutic Response to Antiemetic Agents in Radiation Sickness

	Number of				
Dimenhydrinate (Dramamine)					
Beeler et al	82	26		58	16
Defoe et al	100	—	46	—	54
Walker	22	36		50	14
	204		66*		34
Chlorpromazine (Thorazine)					
Moyer et al	40	70		20	10
Marks	84	81		14	5
O Connell	38	53		39	8
	162	72		22	6

Per cent of patients benefited with therapy

particularly well to Thorazine, but intestinal obstruction must be ruled out before antiemetic therapy is instituted

Even though the specific cause of uremic vomiting is not known, Thorazine has simplified its management Following an initial intramuscular dose, most uremia patients are able to take subsequent doses and nourishment orally within a few hours The unpredictable cardiovascular reactions that sometimes follow intravenous administration of Thorazine contraindicate this route in patients with severe renal disease

The antiemetic agents have become established in treating radiation sickness (Table 21) Dramamine (approximately 400 mg per day in divided doses) provides an excellent therapeutic response in about one third of the mild cases, but approximately as many fail to benefit Benadryl has been reported to give excellent results in about 50 per cent of the patients, with about 10 per cent failures The optimal oral dosage is 50 to 100 mg, 3 times a day, and 50 to 100 mg intravenously if the parenteral route is necessary Thorazine has outstanding value in

these cases and, although the optimal dosage should be determined on an individual basis, 10 to 25 mg, 4 times daily usually suffices

Postoperative Vomiting —Although improved techniques in anesthesia have tended to reduce postoperative vomiting, it and the ensuing electrolyte imbalance wound disruption, and aspiration of vomitus may still cause great distress to the patient The place of antiemetic agents in solving the problem of postoperative vomiting remains undefined Yet, no matter what the complex etiology, the end result of postoperative vomiting is stimulation of the medullary vomiting center Probable causes of postoperative vomiting are

1 Irritation of the gastrointestinal lining Traction on the abdominal viscera may also excite the vomiting center through this afferent visceral reflex arc

2 Blood borne chemicals

3 Cerebral and psychic factors

4 The efferent pathways of the vestibular sense organ, which traverse the *chemoreceptor* trigger zone and may be important in causing postoperative vomiting Morphine derivatives apparently lower the vestibular threshold increase the excitability of the medullary vomiting center, and make it more susceptible to subthreshold stimuli

5 Dehydration and acidosis which predispose to postoperative vomiting

Moore and his associates using a prophylactic intramuscular dose of 50 mg of Dramamine before surgery and following with four 50 mg doses reduced the incidence of postoperative vomiting from 23 to 13 per cent irrespective of the type of premedication anesthetic agent, method of anesthetic administration or post operative therapy Intravenous Dramamine also reduced the incidence and the severity of vomiting markedly but failed to alter the nausea Prolonged drowsiness tachycardia and respiratory depression are the common side effects of Dramamine administration Benadryl has also been reported to be a successful prophylactic for postoperative vomiting (Fig 9)

In the use of Dramamine as a *therapeutic agent* (rather than prophylactic) in postoperative vomiting the effectiveness compares favorably with that of the other antiemetic agents, but Thorazine appears to be more potent in this respect

Generally, Bonamine and Marezine have not been as successful as Dramamine and Benadryl in preventing postoperative vomiting (Fig 9), although Didier and his associates observed equal efficacy with the administration of 50 mg of Marezine

Thorazine is effective in the prevention of postoperative vomiting Its chief indication in this respect is therapeutic in the patient in whom less potent agents (also agents with less side effects) have been ineffective in the prevention of nausea and vomiting Thorazine potentiates the action of sedatives, analgesics, and anesthetics more than other antiemetic agents, and thus smaller quantities of these drugs are necessary This action, in itself, partially decreases the incidence of postoperative vomiting

In one study we gave 12 5 to 25 mg of Thorazine intramuscularly to 90 patients about 45 minutes prior to induction of general anesthesia Only one patient vomited in the postoperative period Blood pressure depressions were frequent but

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acidity predisposes to vascular endothelial damage Because of the occasional hypotensive response I prefer not to use Thorazine intravenously

The likelihood of response to antiemetic drugs should be weighed against the possibility of untoward reactions in each patient It seems logical that Dramamine should be used as a prophylactic measure Then should nausea and vomiting occur postoperatively Thorazine or Marezine should be given Of course, if potentiation of anesthesia is desirable, Thorazine is the preanesthetic agent of choice

Nausea and Vomiting of Pregnancy—Although the exact etiology is unknown endocrine, nutritional, and psychogenic factors appear to be important in inducing nausea and vomiting during the first trimester of one half to two thirds of all pregnancies While oral antiemetic medication and other symptomatic therapy are usually the best prospects, serious cases require hospitalization and treatment with parenteral fluids and other more drastic therapeutic measures

The results of comparable studies of the drugs commonly used in this country show that at least 20 per cent of the patients treated with Dramamine remain unimproved, and short duration of action, prominent side effects, and relative impotency make this drug comparatively unsatisfactory Benadryl has also been

Table 23 Nausea and Vomiting of Pregnancy Comparison of Effectiveness of Antiemetic Agents

Drug and Author	Dose* (mg)	No of Patients	Therapeutic Response† In Per Cent Excellent	Good	Failure
Dimenhydrinate (Dramamine)					
Carliner et al	50 100 t i d	43	72	—	28
Cartwright	50 100 b i d	106	23	46	31
Subtotal		149	37%	33%	30%
Meclizine (Bonamine)					
Bass	25 50 h s ‡	182	90	8	2
Lebherz and Harris	25 h s	92	82	10	6
Mulhern and Bryan	25 h s	100	64	24	12
Subtotal		374	81%	13%	6%
Meclizine + Pyridoxine (Bonadoxin)§					
Weinberg and Werner	1 tab b i d	100	30	58	12
Tartikoff et al	1 tab h s	68	93‖	6	1
Groskloss et al	1 tab h s	287	91‖	5	4
Crawley	1 tab h s	65	82‖	12	6
Baker	1 2 tab h s	50	92‖	6	2
Bethea	1 2 tab q d	46	48	41	11
Fox	1 2 tab q d	150	85	9	5
Subtotal		766	79%	16%	6%
Chlorpromazine (Thorazine)					
Moyer et al	25 q i d	78	71	24	5
Benaron et al	10 50 t i d q i d	114	51	33	16
Subtotal		192	59%	30%	11%

*Signifies oral administration q d = daily h s = at bedtime b i d = twice a day t i d = 3 times a day q i d = 4 times a day

†Therapeutic response excellent = complete alleviation of nausea and vomiting good = vomiting controlled but nausea continued poor = no improvement in nausea and vomiting

‡Supplemented with 12 5 25 mg upon awakening or at noon if necessary

§Bonadoxin contains 25 mg meclizine and 50 mg pyridoxine

‖Includes patients responding in the first week of treatment

minimal excitation, and reflex responses were elicited within one hour after termination of anesthesia Significant and alarming blood pressure reductions seem to have been overemphasized by some investigators For example, Albert and Coakley found that patients undergoing anesthesia without the prior administration of chlorpromazine showed an equal reduction in blood pressure as compared to those patients who received chlorpromazine (Table 22)

*Table 22 Blood Pressure Response to Preoperative Medication With Chlorpromazine (50 mg)**

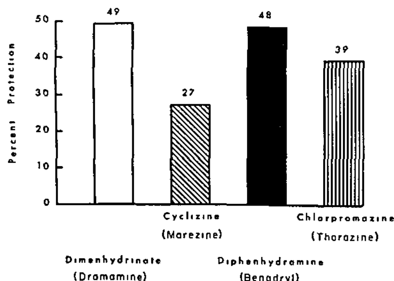


Fig 9
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effective ag
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Drugs M

Morris and associates described only 2 failures when using 12 5 to 25 mg of Thorazine in 23 patients who vomited following spinal anesthesia They found depressions of the systolic blood pressure greater than 20 mm Hg in 9 cases In 7 other cases nausea and vomiting were purposely induced by brief traction on the stomach After Thorazine was administered (12 5 to 25 mg intravenously), patients became refractory to subsequent tugs

Intravenous use of Thorazine requires dilution of the solution because its

Table 24 Recommendations for Antiemetic Therapy

Source of Emesis	Recommended Agent	Dose (mg)*	Frequency
Drug Induced			
Digitalis	Thorazine	10 25	q i d
Antibiotics	Thorazine	10 25	q i d
Nitrogen mustard	Thorazine	25 50	q i d
Alcoholic states	Thorazine	50 150	q i d
Opiates	Bonamine,	25 50	b i d
	Marezine, or	50	q i d
	Dramamine	100	q i d
Infections	Thorazine	10 25	q i d
Toxicoses			
Diabetic acidosis	Thorazine	10 25†	q i d
Uremia	Thorazine	10 25†	q i d
Carcinomatosis	Thorazine	10 25†	q i d
Radiation sickness	Thorazine	10 25†	q i d
Other	Thorazine	10 25†	q i d
Postoperative Vomiting			
Prophylactic	Dramamine	50	t i d q i d
	Benadryl	50 100	t i d -q i d
	Marezine	50	t i d
Therapeutic	Thorazine	25 50‡	t i d
Pregnancy	Bonamine (with or without pyridoxine)	25 50	bedtime

*Refers to oral dose, parenteral doses are usually slightly less
†May increase dose to 50 mg if necessary to arrest vomiting
‡First dose usually administered parenterally

SUMMARY OF THE THERAPEUTIC USE OF ANTIEMETIC AGENTS

The current concepts of the emetic mechanism have been summarized and the pertinent pharmacodynamics of the useful antiemetic agents have been reviewed briefly An outline for their use is presented in Table 24

Thorazine appears to be the most useful agent in drug induced vomiting and vomiting associated with various toxicoses However, Dramamine, Bonamine, and Marezine are probably more effective in suppressing the emesis resulting from opiate administration Parenteral administration of antiemetic agents should usually be reserved for patients who are unable to tolerate oral medication subsequent doses may often be given orally

The prophylactic use of Dramamine and Benadryl appears to offer more protection from postoperative vomiting than Thorazine The frequency and severity of side reactions preclude the routine use of Thorazine, except therapeutically, for control of vomiting in the postoperative period

In treating the nausea and vomiting of pregnancy, Bonamine (with or without pyridoxine) appears to be the most useful antiemetic agent, and at least 90 per cent of the patients improve under this medication Again, Thorazine should be reserved for those whose pernicious vomiting does not respond to other therapy

NEW ANTIEMETIC AGENTS

Thioperazine (Vontil), which is a derivative of phenothiazine, is now undergoing clinical trial The preliminary data available at this time would indicate that

reported to exert a protective action in this syndrome, but in our experience is no more effective than Dramamine

Bonamine is especially effective and has the advantages of a long duration of action (up to 24 hours) and a minimum of untoward side reactions The optimal dose, 20 to 50 mg at bedtime, can be supplemented with 25 mg on awakening or at noon The combination of 50 mg of pyridoxine (vitamin B_6) with 25 mg of Bonamine may also be useful, for pyridoxine supposedly exerts a beneficial ketolytic effect The proportion of patients obtaining an excellent response (complete cessation of nausea and vomiting) with Bonamine, with or without pyridoxine is greater than that with Thorazine or Dramamine Also, there are fewer therapeutic failures when patients are treated with Bonamine than with the other drugs Drowsiness the only common side effect of Bonamine administration usually decreases as therapy is continued and is usually proportional to the size of the daily dosage

The use of Thorazine demonstrates an equally good response rate However the untoward effects of Thorazine—sedation, orthostatic hypotension, and dizziness—are a disadvantage, even though they diminish after a week of treatment The relatively short duration of action also creates therapeutic problems in treating morning sickness, since the bedtime dose has usually worn off Patients who are unable to retain the first daily oral dose must be given this dose intramuscularly or rectally or else take a 2 A M dose Twenty five milligrams (usually given 3 to 4 times daily) is the minimal consistently dependable dose, but a few patients respond to 10 mg Thorazine gave excellent or good therapeutic results in a series of patients with hyperemesis gravidarum, in intramuscular doses of 25 to 60 mg given 2 or 3 times daily It is in the patient with severe, persistent vomiting that Thorazine is the agent of choice

Given intramuscularly in 25 mg doses every 4 hours, Thorazine also reduces the nausea and vomiting occasionally seen during labor and delivery Karp and her associates found that synergistic action made it necessary to reduce the amount of analgesics and anesthetics used in delivery by about 50 per cent Thorazine acts successfully without depressing the fetus or the mother and also reduces the psychomotor agitation and hyperactivity associated with scopolamine

Compazine (prochlorperazine), an analogue of chlorpromazine, is currently under clinical trial as an antiemetic It is more potent than chlorpromazine, and when used in doses of 15 mg or less 4 times a day, it shows promise for the treatment of nausea and vomiting of pregnancy However, larger doses cannot be employed for outpatient and office practice due to the sharp increase in the incidence of side effects when this dosage range is exceeded

It appears that a dose of 10 mg, given orally, 4 times a day, is adequate in the majority of patients In a minority, 5 mg, 4 times a day, will apparently suffice If 10 mg, 4 times a day, is not adequate, the dose can be increased to 15 mg with impunity The drug should not be given intravenously for the treatment of nausea and vomiting The parenteral route is indicated primarily for initial medication in order to arrest emesis following which the oral route may be employed It is best to use the least amount of any of these drugs which will produce the desired response

Hofstron, J E, and Nurnberger, C E Irradiation Sickness Histamine Effect Treated

J Obst & Gynec 69 780, 1955

Kelsey, J R, Moyer, J H, Brown, W G, and Bennett, H G Chlorpromazine Jaundice

Lebherz, ausea and

Marks, J er Causes

Mitchell, 229 363, 1955

Moore, D C, Bridenbaugh, L D, Green, J C, Piceioni, V F, Adams P S, and Lindstrom C A The Use of Dramamine to Control Postoperative Vomiting, J A M A 159 1342, 1955

Morris, G C, Jr, Mathews W, and Moyer, J H Clinical Experience With Chlorpromazine in Spinal Anesthesia Anesth & Analg 33 340 1954

Moyer, J H, Kent, B, Knight, R W, Morris, G, Dizon, H, Rogers, S, and Spurr, C Clinical Studies of an Antiemetic Agent, Chlorpromazine, Am J M Sc 228 174 1954

Moyer, J

O Connel

Scurr, C

Stephen,

Walker,

Wang S nization of the Central Emetic f Apomorphine, Copper Sulfate

Wilson of Thioperazine in Nausea and Vomiting Due to Disease States and Chemotherapeutic Agents Antibiotic Med 6 421 1959

it is approximately 50 times as potent as chlorpromazine and 10 times as potent as triflupromazine, perphenazine, and prochlorperazine

Early observations have indicated that drowsiness and hypotension are not observed in the therapeutic doses needed for severe vomiting Also, whereas signs of extrapyramidal irritation have been observed in dogs, these have not been observed in humans

When used prophylactically by mouth to prevent drug-induced nausea and vomiting, it is quite effective at 0 5 mg every 6 hours However, on occasion a dose of 1 mg every 6 hours may be necessary In severe vomiting it would be wise to administer at least the initial dose intramuscularly In one instance of severe vomiting due to widespread abdominal carcinomatosis and the administration of an anticarcinogenic agent, the patient received only partial relief from 1 mg intramuscularly every 6 hours but was completely relieved of vomiting and almost completely relieved of nausea on a dose of 1 5 mg every 6 hours Even at this dose level there was no evidence of side effects

Evaluating New Antiemetic Agents.—When evaluating new antiemetic agents, it is necessary to pay close attention to the associated effects on the central and autonomic nervous systems The aim is to find agents which will specifically depress the emetic mechanism with minimal effects elsewhere It is apparent that the more potent the antiemetic activity of any drug, the more likely that other (untoward) effects on the central nervous system will develop These effects can be insidious and obscure to the observer but devastating to the patient, particularly is this true of depression, anxiety, and agitated depressive reactions

SELECTED REFERENCES

216, 1951

Conner, P K, McConn, R., and Moyer, J H An Attempt to Alleviate the Emetic Effect of Protoveratrine by the Concurrent Use of Chlorpromazine in the Treatment of

1947, Suppl 4

must also be an understanding of the probable basis of their effects in the obe patient

This is of course, no place to go deeply into the psychologic basis of obesi or the symbolic implications of overeating It is sufficient to accept the uniform stated opinion of experts that all cases of obesity not explainable on an organ or cultural basis are psychogenic, and that the psychogenic comprise over 9 per cent of the total Beyond this, there is *the important fact that, regardless* o what measures are used to help the obese lose weight, unless something positiv is done about the psychologic factors involved, when treatment stops, lost pounc age will soon make its way back

Stunkard states that most obese patients will not stay in treatment for thei obesity, that of those who do, most will not lose weight, and of those who los weight, most will regain it There is his discouraging experience that of 1 of *100* patients who lost more than 20 pounds under his care, after a year, half ha *recouped their hard* won losses, and within the second year there remained onl 2 who were not plump once more This means that after 2 years of treatmen only 2 patients out of 100 showed any benefit from treatment

More than half of obese patients on weight reducing regimens suffer som psychic reaction, and half of these are severe emotional disturbances Stunkar *noted that the night eating" syndrome often complicates otherwise successfu* treatment for obesity This syndrome, which is a response to stress which appear in other situations as well consists of insomnia, nocturnal pangs of hunger, an morning anorexia No part of this is a specific pharmacologic reaction to drug which are used to depress appetite, rather it is all part of a psychologic reactio to a regimen which deprives patients of a form of support of deep psychic and symbolic significance, overeating This speaks volumes for the importance of the psychologic background of the condition as well as the intensity of the psychologic resistance (despite all apparent desire for weight loss) *to measures* which decrease food intake

Lesses and Meyerson feel that the obese suffer from anhedonia, that is to say that, although there appears to be a compulsive drive to eat, the act of eating, no matter how excessive, provides neither satiety nor satisfaction As a corollary, *therefore simple appetite depression would have little useful effect,* for appetite per se has nothing to do with it Although this may seem unusual, it is not really different from the plight of most alcoholics, many of whom often do not really enjoy the effects of alcohol and very much wish *to stop drinking,* but who, never theless, consume inordinate amounts of alcohol often very rapidly, and appear to take little or no pleasure in what seems to be a purely compulsive act

Mayer has suggested a metabolic or 'glucostatic" mechanism which *normally* controls appetite and hunger, others have suggested a hormonal mechanism which controls intestinal activity which is related to the hunger drive, and still others have suggested a center in the nervous system for its control We should like to press our view that whatever the mechanism of the normal psychologic control of appetite may turn out to be, these are *likely to have little to do with the problem* ... normal 'appestat' setting of a

THE CHOICE OF AN ANOREXIANT

Walter Modell, M D , and

George G. Reader, M.D

INTRODUCTION

For cultural and cosmetic reasons as well as for reasons of health, there has been great pressure on both our male and female population to shrink its diet as well as its waistline In a country with so much good food so easily obtained, mass efforts in this direction have been notably unsuccessful As a result, some easier way out has been sought, e g , a drug which would assist by depressing the appetite, hence, the recent interest in anorectic agents, of which there are a number now on the commercial drug market and about whose actions and virtues there is little precise information

In practice, the so called anorexigenic drugs are not used simply to depress the abnormal appetite, for even if there is marked bulimia or polyphagia, these drugs are not given unless there also is obesity Thus the problem of the use of these drugs is inseparable from the problem of obesity and its causes, and any attempt to consider the question of their choice on a strict pharmacologic basis as primary anorexigenic drugs is unrealistic

The designation "anorexigenic' to a particular group of drugs in common use is perhaps unfortunate because it implies a precise pharmacologic action on the central nervous system which has never been demonstrated and, as a matter of fact, direct depression of the central appetite controlling mechanism is never even examined in the clinical studies on the anorectic effects of drugs What these reports actually attempt to examine is a therapeutic accomplishment in the obese, loss in weight without toxicity, which is, of course, also the result in which the practitioner is interested Nevertheless, the group of drugs used in the treatment of obesity is now saddled with this inappropriate but highly suggestive term, and, as a consequence of its unsubstantiated implications, studies of the mechanisms involved have been obscured by it and, in our opinion, the treatment of obesity is all the worse for it

CLINICAL CONSIDERATIONS

As matters now stand, these drugs are used exclusively in the relief of obesity and, to choose from among them as well as to apply the choice effectively, there

It is interesting in this connection that, if these drugs were specific anorexiants and if their supporters really felt so, it would not be necessary, as all of them seem to find, to put patients on restricted diets If their appetites were, in fact depressed by the drugs, what always happens when appetites are really depressed would also happen in this case, the obese patients would eat less regardless of how much was available In these cases, the patients usually eat less only if less is available It seems clear, therefore, that, despite their stated enthusiasm, even the staunchest supporters of the anorectic drugs are basically insecure about the anorectic effects of these drugs We suggest an examination of a patient with loss of appetite after overdosage with digitalis for a view of the phenomenon of a truly depressed appetite

Most of a large number of studies on the effects of the so-called anorexiants in man indicate clinical effectiveness, and only a few suggest that they are of limited value or of no value at all On the other hand, those that do recommend the use of appetite depressing drugs all seem to agree that the drugs are only a crutch and should be used only for a limited period of time Whereas many of the studies on anorectic drugs currently available have indicated, by one means or another, that their use is associated with weight loss, most of these studies have no useful controls whatever, resting their case entirely on the fact that patients lost weight after taking the new drugs, and overlooking the common experience that a large proportion of obese persons tend to lose weight on entering any new treatment or even an association with a new physician In other studies that use a placebo, a difference in the weight loss after the placebo vis a vis the drug, is taken as evidence of the effectiveness of the drug in question In a relatively few instances, a double blind scheme is used to remove bias, and in a few of these a cross over plan is used so that each patient is used as the basis of comparison for his weight loss after the anorexiant

Many studies have indicated that within 30 minutes of the taking of the modern anorectic drugs the subjects clearly experience a "lift," as improvement in the sense of well being, wakefulness, a tendency to increased activity This being the case, even where the double blind technique is used to start, after 30 minutes the patients know which is medication and which is placebo, and only the physician remains blind After 30 minutes there are, therefore, neither double blind nor placebo controls, and all the psychic impact of the knowledge that an effective drug is being taken is exerted in favor of the drug being tested From this point of view, therefore, there have yet been no double blind studies, for a difference between the effects of the placebo and the drug in these studies may well be due to the *detection* of this difference by the patient and not due to the *action* of the drug itself

While some designs undoubtedly make a sterner attempt than others to control the experiment, the fact remains that none of them are properly controlled to eliminate or take into account the well established influence of suggestion and the offer of a crutch to the obese patient about to embark on the trial of refraining from overeating This is not the place for a thorough analysis of the many reasons which may invalidate the conclusion that none of these positive results after the taking of the anorectic drugs prove a specific anorectic action

The long term results of weight loss therapy are very poor at present What is urgently needed for the effective treatment of obesity is more understanding of the reasons why the obese continue to eat without reference to situation Failing this an anorectic agent is likely to have as little effect on the over all problem of obesity as Antabuse (disulfiram) has had on the over all control of alcoholism In the face of a compulsive desire to overeat, none of the anorexiants are effective unless food intake is controlled as well hence it is obvious they are not very effective against this force It is clear that in most instances of resistive obesity therefore psychotherapy of some sort seems the most logical therapy, and, as a matter of fact the best (over 50 per cent improvement) as well as the most durable results reported have been after psychotherapy of some type and not through the use of drugs

PHARMACOLOGIC CONSIDERATIONS

Anorexiants have long been known Anorexia is a common effect of drugs, e g digitalis even sodium chloride may induce nausea and thereby reduce the desire for food in even the most compulsive of eaters The reputed search for an effective anorectic drug therefore is not really for a drug which depresses appetite but rather for one in which this effect is dissociated from distress and discomfort This makes matters difficult, since even in the obese, drug action inducing nausea can be counted upon to continue to depress appetite without the development of tolerance whereas tolerance does develop after the use of the so called anorexiants now in use

The search for a useful anorectic agent is further complicated by the fact that an effect is sought on a singularly human trait, the tendency to overeat The abnormal drive for food in man with its symbolic overtones and its psychologic complications may not be satiated by amounts of food which ordinarily satisfy the appestat drive a pathologic situation not duplicated in the laboratory animal Since the special communication necessary to indicate the pure anorectic state sought is not within the capacities of the laboratory animal (although we sometimes can distinguish nausea in the cat and dog) simple anorexia without nausea or other distress which may distract the appetite cannot be determined or explored in the laboratory animal While it is a fact that by damaging the brain some laboratory animals have been made to overeat this does not correspond to the situation in the obese patient who overeats with an undamaged and so far as we know a functionally normal brain

Most of the reports of studies of the anorectic drugs on the drug market based on animal experimentation uniformly indicate decreased food intake and loss of weight In these instances however not only is it impossible to compare the dosage used in the animals with that which may be used with safety in man but it is also impossible to compare the biologic effects induced or to say what minor distresses the animal might have suffered to induce the anorexia Since anorexia in the animal may well mean something other than what is sought in man regardless of apparently desirable or meaningful effects in animals only the experiment in man provides the final answer to the complex issues involved in the relief of obesity in man

even new but, in the case of Benzedrine, is perhaps not overshadowed by other dramatic pharmacologic actions and hence is more obvious At present in the same group of drugs there are also dextro amphetamine (Dexedrine), metamphet amine (Desoxyn and about 30 other proprietary names), phenylpropanolamine (Propadrine), phenmetrazine (Preludin), phenylbutylamine resin (Ionamin) diethylpropion (Tenuate Tepanil) and Levonor (levo amphetamine alginate), which are promoted and used clinically as anorexiants (Despite disclaimers in advertisements it is easy to demonstrate that all really belong to the same pharma cologic group of drugs as Benzedrine)

As explained previously, it is by no means definite that these drugs have any primary effect on the appetite at all and there is a strong suggestion that they may assist in the reduction of weight through other and entirely different pharmacologic actions in the central nervous system There is reason to suppose that the anorectic effect is due to an action on the higher centers rather than on any appetite control center situated lower in the central nervous system e g pa tients who have bulimia after frontal lobotomy are not affected by these drugs

In varying degree all the amphetamine like drugs induce central stimulant effects wakefulness increased mental and physical activity and in some instances excitement and agitation Many patients clearly experience a 'lift Nor can these be properly termed side effects if it is the cephalotropic action that is the basis of their effect in obesity and if it is due to a sense of well being and elation that subjects under an emotional drive which makes them overeat are better able to accept dietary restrictions There has been described as well a loss of acuity of olfactory and gustatory sensibility which may be an additional factor in the so-called appetite depression The amphetamine like drugs are of no value for the night eating syndrome since their action to induce insomnia contraindicates their use late in the evening or before retiring

Although there have been some deaths from these drugs in general they are not dangerous and relatively few cases of acute poisoning or serious reactions have been reported as the result of their large scale and continued use Aside from the indirect consequence of prolonged insomnia the most serious complication is de pendence On the other hand tolerance may develop so that such effects as they may induce are likely to be relatively short lived while in order to continue the effects doses must be increased, a procedure which tends to increase disagreeable side effects especially nervousness and insomnia The drugs therefore are not useful for prolonged therapy

As sympathomimetic amines the effects on the cardiovascular system are im portant A rise in blood pressure and the tendency to palpitations are often mat ters for serious consideration Aside from the probable high incidence of such effects from Benzedrine (amphetamine), there is little to choose among the others and in them a proper fitting of drug and patient often has to be made by trial and error on an individual basis

The history of most of the drugs listed below is remarkably similar—a wave of enthusiasm for it followed by a wave of enthusiasm for the next newcomer to the same series

The fact that the sensations produced in the central nervous system by the mod n anorectic drugs are very impressive is of importance to patients anxiously eking a crutch to help them lose weight That they appreciate some sensations fter taking a drug proves to them that they are getting medical assistance This rutch therefore means more to them than the mere taking of an inert placebo— this case an *ert* placebo seems to have special ancillary pharmacodynamic ctions worthy of further study

The effect of the so called anorectic drugs on the psychic state of the obese atient has not been examined carefully in the case of the more recently introduced nembers and while such an action is disclaimed or by implication denied the igh incidence of wakefulness and other central nervous system stimulant actions trongly suggests that such an action may be a regular if not the only important ne Should these drugs provide the sort of lift for which amphetamine has ong been used it may indeed be a bulwark for the obese and provide a sub itute for overeating It may also explain the limited value of these drugs

There are other interesting implications in one of the effects on the central ervous system which have been reported There is clear evidence, in animals s well as in man that beyond a certain norm decreased physical activity in reases appetite and vice versa increased physical activity decreases appetite This applies to the obese person as well as to the thin person Increased activity s the common symptom often termed a side effect of the anorexigenic drugs It may well be therefore that in addition to the calorigenic effect of increased hysical activity due to these drugs there is decreased intake as a concomitant nd if this is so the anorexiants may be associated with a weight loss through a entral stimulant action rather than a primary anorexic action Stunkard has ndicated that limited physical activity may be a more important feature of besity than is generally appreciated and it may be that this is an important action f these drugs in some weight loss studies and that the primary effect on the appetite enter so many prefer to ascribe to them is of little importance

THE SEVERAL DRUGS

Amphetamine like Drugs

There is an erroneous but widespread impression that amphetamine sulfate Benzedrine) was the first of a series of anorectic drugs leading to the development of the most recent analogue diethylpropion (Tenuate Tepanil) As far back as 1889 etrahydrobetanaphthylamine was synthesized and was soon recognized to have both sympathomimetic and cephalotropic as well as calorigenic actions Because of toxic effects, interest was lost in tetra," and even though some work with *he drug continued into the first decade of the twentieth century, the similarity* n its actions and structure to the recognized sympathomimetic amines was gen rally ignored

The cephalotropic action of the amine drugs closely related to epinephrine and ephedrine was early recognized as a complication of their clinical use Despite this, in the case of amphetamine, this action was emphasized as both a new and a unique one It is now abundantly clear that this action is neither unique nor

flood of publications on the results of trials with a new drug Like the reports for the others they indicate that phenmetrazine is an effective anorectic agent. Some publications indicate that soon (30 minutes) after administration many patients appreciate cephalotropic actions This vitiates any attempts at placebo and double blind controls and strongly emphasizes the psychic factor in the apparent results from the drug Phenmetrazine appears to have little or no important effect on the cardiovascular apparatus Whether its apparent desirability is due to its relative impotence or because of a specific action remains to be demonstrated Despite statements to the contrary, Preludin belongs to the amphetamine group of drugs

Phenylbutylamine Resin (Ionamin)—Through exchange with electrolyte this resin releases phenylbutylamine, an amphetamine congener, in the gastrointestinal tract All systemic effects, therefore, stem from an amphetamine like action. There is too little experience with this agent for a final evaluation of its position in the therapy of obesity

Diethylpropion (Tenuate, Tepanil)—This amphetamine congener has just been put on the commercial drug market There is insignificant evidence published thus far but no reason to hope that it is at all superior to dextro amphetamine

Summary—Largely because the problems involved have not been dissected and because the probable role of the sympathomimetic amines in the treatment of obesity has not been defined, there is no clear basis for indicating which of these drugs for whatever it may contribute is the best It is reasonable to suppose however that, since elevation in blood pressure and cardiac acceleration are not useful in any case and may sometimes be harmful, levo amphetamine sulfate and phenylpropanolamine are clearly the least desirable The history of these agents is that notions of superiority regularly disappear with accumulating experience but as matters now stand, it may be taken that dextro amphetamine is probably the most desirable of the lot

Calorigenic Agents

About 25 years ago, dinitrophenol which increased metabolic rate without inducing the sensation of heat commonly complicating the use of thyroid materials had a brief period of trial Weight was lost by many who tried it but because of the report of the development of cataracts, the use of the drug was abruptly discontinued No drug with similar calorigenic effects is now in use

Thyroid and Related Materials—It has long been recognized that increased thyroid activity causes loss of weight despite increased ingestion of food This seems to provide an approach to the treatment of obesity which avoids the difficult problem of depressing the appetite of the obese, and, with this aim in view thyroid materials have been used in obesity Unfortunately, unless deficiency in thyroid function is the basis for the obesity the approach ultimately fails And it fails just as frequently, whether the old fashioned desiccated thyroid or the newest form liothyronine (Cytomel) is used Neither is recommended nor is any intermediate between the two In addition to their over all ineffectiveness the thyroid materials may lead to intense nervousness, insomnia discomfort due

Amphetamine (Amphate, Bar Dex, Benzedrine, Dietamine, Monophos, Profetamine, Racephen Raphetamine) —The cardiovascular effects of this drug (racemic and levo forms) are likely to be disturbing therefore amphetamine has limited value in obesity and is rarely used today

Dextro Amphetamine (Dexedrine) —This agent which is the dextrorotatory form of amphetamine differs from the racemic and levo forms in that while the cephalotropic actions are well developed the cardiovascular effects are much feebler This relative segregation of effects makes this the more desirable where as in obesity the cephalotropic actions alone are needed This also serves to emphasize the importance of the cephalotropic actions of these drugs in obesity

Levo Amphetamine Alginate (Levonor) —The alginate of the levo amphetamine is so much feebler with respect to both cephalotropic and cardiovascular actions than amphetamine sulfate that the doses used are virtually if not entirely inert This is due to the fact that the alginate comprises the bulk of the molecule so that a 5 mg tablet of Levonor contains only about one third as much amphetamine as a 5 mg tablet of the sulfate of amphetamine It is the most recently introduced weight reducing product and therefore there is little clinical experience to indicate whether this reduction in potency has any advantages over that which could be obtained with a proportionate downward adjustment in dosage of the sulfate of amphetamine It is our opinion that in the doses recommended there is little difference between this agent and a placebo

dl Amphetamine Resin Complex (Biphetamine Resin) —The complexing of dl amphetamine with resin may prolong its action Whether it also segregates the cardiovascular from the cephalotropic action is doubtful and on this basis it would not appear to have any special pharmacodynamic advantage Whatever action it has tends to be prolonged and therefore should it be demonstrated to have useful effects it could probably be given less frequently than dl amphetamine

Methamphetamine.—The only feature which distinguishes this analogue of amphetamine from amphetamine itself is the exceedingly large number of trade names under which this material is sold namely Amphedroxyn Apamine Deofed Desamine Desoxedrine Desoxo 5 Desoxyephedrine Desoxyn Desyphed Detrex Dexoval Dexstim Dexoval D O E Doxyfed Drinalfa Efroxine, Lanazine Methamphin Methedrine Methoxyn Miller Drine Norodin Oxyfed, Oxydess Premodrin Normadrine Norodin Semoxydrine Stimdex Syndrox There is no evidence that its action differs from that of amphetamine in any way except that the action on the cardiovascular system is somewhat less intense and the action on the central nervous system is somewhat more intense

Phenylpropanolamine (Propadrine) —The vasoconstrictant action of this drug tends to elevate blood pressure and thereby limits its usefulness in the treatment of obesity While it is used in over the counter remedies for obesity such as Regimen tablets Du Dol and ℞ 121 the amount of phenylpropanolamine which they contain is too small to exert any pharmacologic effect at all

Phenmetrazine (Preludin) —More has been written recently about this agent than any of the others in the group less because of real superiority than because of timing The interval since introduction is just right for the appearance of a

with weight loss It is agreed by those who recommend them that, however they are used and however they may work, they should not be taken for a prolonged period but rather as an adjuvant to a restricted diet in the early stages of the weight-losing regimen There are others who take the view that the assistance these drugs provide may make it even more difficult for the obese to keep to the proper diet after the drug is discontinued The best compromise between these two views is to use the drugs in effective doses for a short period (i e, in doses which induce the cephalotropic effects which probably account for any action which they may exert indirectly on the appetite) and, having accomplished some weight loss with such a program, to discontinue the drug and continue with a maintenance diet At the same time the basic psychologic trouble must be dealt with

It is well to remember that the anorectic drugs in current use do not have the kind of depressant effect on the appetite which will keep the obese from over eating It is necessary therefore, also to prevent patients who are taking these drugs from overeating by some other mechanism, usually a rigidly enforced low caloric diet

WHAT IS NEEDED IN A NEW ANOREXIANT

What is needed in anorectic drugs is not another version of a drug which dis tracts the appetite of the obese person indirectly by means of a stimulant action on the central nervous system, but one which depresses the appetite control mechanism directly, that is to say, a truly specific pharmacologic anorexiant Investigations of such a drug action would probably be better carried out in subjects with normal appetites than in those with the abnormal, complicated, and poorly understood appetite drives of the obese person

What is needed is a drug which will keep the patient from eating too much when too much is available, not one which must be used in conjunction with food restriction This, of course, is a clear indication of the inefficiency of the drugs now used for appetite control

What is wanted is a drug which, when it does depress appetite, neither makes the obese patient ill nor deprives him of the emotional comfort which overeating provides Unless it gives him a substitute comfort, there is certain to be a high incidence of emotional reaction to the regimen itself

What is needed, therefore, is a therapy rather than a drug which with con siderable specificity, corrects the psychic disturbance in the obese person which upsets his appestat" As matters stand, no drug is available which provides it and, in its absence, it seems clear that, regardless of its expense and relative difficulty, for most patients the best approach to obesity is some form of psycho-therapy The best results (about 50 per cent improvement) have come with such methods Since there are many symptoms they suffer in common it would seem that group therapy through an organization similar to Alcoholics Anonymous might provide the best hope for the obese person

SELECTED REFERENCES

Brobeck J R *Neural Factors in Obesity* Bull New York Acad Med 33 762 1957
Brosin, H W The Psychiatric Aspects of Obesity, J A M A 155 1238, 1954

to the calorigenic effect excessive perspiration and palpitations A recent publication apparently favoring the use of liothyronine examined only the effects of a combination with amphetamine hence it provides no support for the use of liothyronine alone

Central Sedation

Inasmuch as obesity often is an expression of some emotional disturbance which may be aggravated by attempts to restrict the intake of food it is not at all surprising that central sedation and tranquilization can sometimes assist in the weight loss regimen If sedation is intense enough to dull mental acuity or induce a degree of sleepiness the appetite drive will be depressed along with other centrally controlled functional activities There is evidence in a study by Ressler that tranquilizing doses of chlorpromazine (Thorazine) (and therefore presumably also of its congeners) may be effective in weight loss Unfortunately the study by Ressler is uncontrolled Sedation and tranquilization may be effective in the case of the night eating syndrome

Bulk Producers

Methylcellulose a nondigestible but otherwise harmless bulky material has been suggested as an appetite satiator for the treatment of obesity This has proved to be no more effective a device for the treatment of obesity than the high residue low calorie diet itself Apparently what the obese want to eat is genuine food the solution is not simply a matter of distending their stomachs with indigestible matter until they can eat no longer

THE CHOICE OF AN ANOREXIANT

The more important decision than the choice of an anorexiant is whether to use such a drug at all All investigators even those who approve of the use of the anorectic drugs agree on the psychologic reasons for obesity in the patients for whom these drugs are designed That being so there is clearly no cure for obesity in the drugs at the very best they provide only a temporary crutch during a brief initial period of dietary restriction Any assistance the medication provides during this period is to be weighed against the letdown the patient suffers when his crutch is removed and he has to face the rigors of dietary restriction while suffering an abnormal appetite drive

Under these circumstances the drug of choice is the one which causes the fewest side effects It would appear that of all the drugs in common use all of them presently belonging to the amphetamine group dextro amphetamine (Dexedrine) seems to be the least likely to induce cardiovascular effects On the other hand it does not seem likely that the cephalotropic actions can be divorced from any value these drugs may have in obesity

REGIMEN FOR THE USE OF ANOREXIANTS

There is evidence albeit not entirely convincing that the use of certain anorexiants all congeners of amphetamine (Benzedrine) is regularly associated

Chapter 22

THE CHOICE OF DRUGS FOR GASTROINTESTINAL DISTURBANCES

Thomas P Almy, M D, and

Herman Steinberg, M D

THE CHOICE OF AN ANTISPASMODIC

Introduction

The term *antispasmodic* is applied to any of a large group of drugs used for the purpose of diminishing motor and secretory activity in the gastrointestinal tract and other *structures supplied with excitatory cholinergic nerve fibers* These properties are found in the natural alkaloids of belladonna, one of which, atropine, is generally used as a standard of reference for the potency of all compounds both natural and synthetic. In the last 20 years a large number of compounds have been synthesized which have similar properties As will be emphasized below, the term antispasmodic is a misnomer, and the adjective *anticholinergic* more truly defines the important action of these drugs

Clinical Applications

Duodenal Ulcer —In this disease the rapid emptying of the stomach and the excessive and continued secretion of hydrochloric acid and pepsin are to a large degree dependent upon vagal stimulation This is especially true of the *inter digestive* and particularly *nocturnal* activity of the stomach For these reasons a 'medical vagotomy" by an anticholinergic drug is a valuable part of the therapeutic program As the sum of the stimuli they must oppose is much reduced at night, they are much more effective when given at bedtime than during the day and they can virtually replace all other methods of control of night secretion in most patients with acute duodenal ulcer

In ulcer with *obstruction*, however, these drugs exaggerate gastric retention and through release of gastrin from the gastric antrum tend to aggravate hyper secretion Thus in the presence of obstruction they are contraindicated

Because extraneural stimulation of the stomach (as by gastrin) is not affected, peptic digestion is seldom completely halted by such a drug, and diet and antacids should still be given As the most potent effect of an anticholinergic upon the

Bruch H Role of the Emotions in Hunger and Appetite Ann New York Acad Sc 63 68 1955

Fazekas J F, Ehrmantraut W R and Kleh J A Study of the Effectiveness of Certain

Gadek F ... nyl 2 Aminopropane

Grossman ... Hunger and Appe

Hamburger ... ork Acad Med 33 771 1957

Harris S C Clinically Useful Appetite Depressants Ann New York Acad Sc 63 121 1955

Leake C ... sher

Lesses M ... Sulfate as

Mayer J ... le Etiology

Modell W ... o

Quigley ... ood Ann

Ressler C Chlorpromazine Therapy in Selected Cases of Obesity New York J Med 57 1607 1957

Ressler C Treatment of Obesity With Phenmetrazine Hydrochloride A New Anorexiant J A M A 165 135 1957

Stunkard A J Untoward Reactions to Weight Reduction Among Certain Obese Persons Ann New York Acad Sc 63 4 1955

Stunkard A J Physical Activity Emotions and Human Obesity Psychosom Med 20 366 1958

Stunkard A J and McLaren Hume, M The Results of Treatment for Obesity A M A Arch Int Med 103 79 1959

Tepperman J Etiologic Factors in Obesity and Leanness Perspectives Biol & Med 1 293 1958

Williams R H Daughaday W H Rogers W F Jr Asper S P Jr and Towery B T Obesity and Its Treatment With Particular Reference to the Use of Anorexigenic Compounds Ann Int Med 29 510 1948

shown to have impressive potency Under clinical conditions the results of their use have been *less striking, apparently* because the neural stimuli they must counter act are more intense and because the effective dose in man is less exactly measured

Disappointments in their use have resulted also from failure to recognize two types of disturbed motor and secretory function of the intestines, which require separate means of control pure *hyperfunction* in normal rhythmic pattern and *dysrhythmia* Hyperfunction, exemplified by *nervous diarrhea and by hypersecre-*tion and rapid emptying of the stomach associated with duodenal ulcer, can be related to excessive cholinergic stimulation, and can be at least partially controlled *by anticholinergics in* adequate dosage Dysrhythmia or *spasm,* on the other hand, represents a disturbed *pattern* of function, with excessive nonpropulsive motility at one or several points This occurs transiently as a result of neural stimulation integrated in the central nervous system (as in nausea or in "mucous colic") It also develops and remains permanently as a result of absence or degeneration of the ganglia of the myenteric plexus, which is essential for the propagation of peri stalsis (as in *cardiospasm, congenital pyloric stenosis or congenital megacolon)* In neither of these circumstances is an anticholinergic drug effective, unless it *abolishes all motor activity It cannot be expected, by virtue of its peripheral locus* of action to restore a normal *pattern* of function

Untoward Effects —The use of effective doses of these compounds in intestinal disorders is accompanied by side effects such as dryness of the mouth and nose flushing and dryness of the skin, cycloplegia, tachycardia, and urinary retention These are the results of blockade of cholinergic impulses to other structures (sali vary glands, ciliary muscle, heart, and bladder) and thus parallel in degree the desired effects on intestinal muscle and glands Despite many claims to the con trary *there is insufficient evidence that in man any of the available drugs of this* class regularly produces a satisfactory blockade of the intestine in the absence of these side effects It therefore seems desirable to use the more minor of these toxic symptoms as indications that an effective dosage has been achieved *In patients* with bladder neck obstruction these drugs are contraindicated because effective dosage invites serious disturbances of vesical function

The Several Anticholinergic Drugs

The important anticholinergic agents include both the natural *alkaloids of* belladonna and a variety of synthetic substances more or less closely related in chemical structure All are substituted amines, while the more active belladonna alkaloids are tertiary amines, the majority of the useful synthetic agents have a quaternary structure The more useful agents are grouped below

The *Belladonna Alkaloids —Two of these preparations are of lasting* value

TINCTURE OF BELLADONNA —One milliliter contains approximately 0 3 mg of mixed alkaloids and anticholinergic effects, lasting 3 to 4 hours, are obtained with 1 5 to 3 ml in the adult patient This permits nice adjustment of the dose The preparation being a crude one, is quite inexpensive but can only be given orally It is thus of maximum value for chronic administration to ambulatory patients

stomach is to reduce its motility and as smooth muscle tension is at least a major factor in the causation of ulcer pain such a drug may abolish ulcer pain while peptic autodigestion continues Presumably as a result of this, painless hemorrhage and acute perforation without premonitory distress have been reported during therapy with anticholinergics

Peptic Ulcer at Other Sites —In marginal (gastrojejunal) and in *esophageal* ulcer the application of anticholinergics is essentially the same as in duodenal ulcer In *gastric* ulcer the influence of vagal stimulation on the stomach is less important than that of the gastrin mechanism and interdigestive secretion and motility are usually low For these theoretical reasons, anticholinergics are less clearly indicated than in duodenal ulcer and may actually increase the level of gastric secretion through promoting antral stasis as in an obstructed ulcer Anticholinergic drugs are recommended only in those cases of gastric ulcer that have a demonstrated high level of acid secretion and rapid gastric emptying

Pancreatitis —In acute pancreatitis and in those phases of acute pancreatic injury which punctuate the course of chronic pancreatitis the gland is affected in two ways by cholinergic stimuli Direct vagal stimulation of the pancreas augments its secretion particularly of enzymes and concomitant hypersecretion and hypermotility of the stomach may lead through sustained acid stimulation of the duodenal mucosa to excessive production of secretin As pancreatic damage develops rapidly and the patient is usually nauseated or vomiting parenteral use of an anticholinergic drug in large dosage is indicated

Diarrhea —Diarrhea associated with functional bowel disorders (called adaptive colitis irritable colon or mucous colitis) is probably related to excessive cholinergic stimulation of the bowel indeed it has been reproduced experimentally with acetylcholine and methacholine Anticholinergic drugs are thus useful and rational adjuvants to the needed psychotherapy in these patients Where diarrhea is associated with *true inflammation* of the bowel wall (e g ulcerative colitis, or salmonella enteritis) they are largely ineffective Their use is not recommended in the *malabsorption syndrome* and in the *postgastrectomy* ("dumping) *syndrome*, where they are not helpful and absorption may be further impaired by their use

Spasm —As explained further below anticholinergic agents may *not* be expected to relieve spasm at various sites unless given in sufficient dosage to terminate all normal motor and secretory activity in the intestine An exception may be made of some examples of spasm associated with absent or degenerate ganglia —thus the painful incoordinated contractions of the body of the esophagus in some patients with cardiospasm can be relieved by these drugs

General Pharmacologic Considerations

The important mechanism of action of these drugs is metabolic competition with acetylcholine at the postganglionic nerve endings in intestinal muscle and glandular acini and to a lesser extent in the ganglia of the intestinal wall thus effecting a partial blockade of extrinsic neural stimulation Under the usual conditions of testing of these drugs in the experimental animal utilizing isolated loops of intestine or intact anesthetized animals a great many compounds have been

dry at least part of the time Such a round-the clock regimen, the same dose being given before each meal and at bedtime, is useful in all of the clinical applications outlined above, if oral medication is possible In acute pancreatitis the same result is achieved by parenteral administration at 4 hour intervals

In other situations it is wise to give a larger dose at that time of day when the drug will be most useful, or even confine the use of the drug to that time In active duodenal ulcer the drug may not be needed during the daytime hours of frequent feedings and interval alkali but will be most useful when given at bed time During the night it acts to reduce interdigestive secretion in the stomach and to prolong the buffering action of the bedtime feeding by retarding gastric emptying Also, adequate doses may not be acceptable to ambulatory patients during the day because of intolerable dryness of the mouth or especially blurring of vision whereas the occurrence of these in even greater degree during the hours of sleep may pass virtually unnoticed In patients with functional diarrhea the most frequent and urgent bowel movements occur from 1 hour before arising to about 2 hours after breakfast Such patients may be advised, for example, to take a large dose at 5 30 A M without getting out of bed, and then try to go back to sleep During the remainder of the day no medication may be necessary

No patient should be given an anticholinergic drug without precautions against the risks of acute glaucoma, bladder neck obstruction, and toxic psychosis The history should be reviewed for delirious reactions to drugs eye pain, conjunctivitis changes in refraction and urinary frequency The tension of the eyeballs and the size and shape of the prostate should be determined by palpation before the drug is given Each patient should be seen a few days later in order to detect early any dangerous effects

Rational Basis for New Anticholinergic Drugs

The numerous anticholinergic drugs in current use have been prepared largely for the purpose of escaping the unpleasant side effects of atropine, methantheline, and other potent compounds This has not been achieved except in minor degree yet there are many who believe that pharmacologic action is so specifically related to chemical structure that compounds can some day be prepared which act upon cholinergic nerve endings in the intestine but not in the bladder, the salivary glands and the eye Such specificity would certainly be desirable if achievable

The other limitation of presently available anticholinergic drugs is that in order to combat excessive secretion and motility the dose must be large enough virtually to abolish normal cyclic or rhythmic activity Thus diarrhea is unlikely to be controlled without producing intestinal stasis, and this is probably due to the site of action of these drugs, at the periphery of the autonomic nervous system True antispasmodic activity, in which normal cyclic activity is restored can probably be obtained with drugs acting upon the integrating centers in the central nervous system The only known example of such activity is that of the anti emetic drugs (see page 325) which abolish the duodenal spasm associated with nausea and permit a return to normal rhythmic motility Study of other drugs capable of depressing cerebral visceromotor centers may uncover useful agents which more nearly satisfy the desiderata of 'antispasmodic' action

ATROPINE—In tablets of 0 5 mg, the pure alkaloid can be given in doses of 0 5 to 2 mg orally or subcutaneously to produce varying intensities of anti cholinergic effects lasting 3 to 6 hours The dose is less easily adjusted than with tincture of belladonna and hence atropine is not as useful in the management of milder, chronic gastrointestinal syndromes, such as irritable colon where toleration of side effects must be considered In patients with more severe and acute illness (e g penetrating duodenal ulcer, or pancreatitis) the severity of side effects is less important, and the more prompt and dependable action of the pure alkaloid par ticularly when injected hypodermically makes it more desirable

None of the other preparations of belladonna or its alkaloids find widespread use as systemic anticholinergics

The Synthetic Anticholinergic Drugs—These compounds mostly quaternary amines have appeared in large numbers in recent years Most of them combine the postganglionic anticholinergic activity of atropine with some degree of gan glionic blockade The vast majority have well demonstrated potency in experi mental animals A number of them have been shown by objective testing in man to inhibit motility and secretions of stomach and intestine more strongly than atropine when given in doses producing comparable dryness of the mouth blur ring of vision and other side effects For this reason they are preferable to atro pine for most gastrointestinal indications in spite of considerably greater cost There are considerable differences in the amount and quality of clinical experi ence and physiologic study in man on which are based the recommended doses of the various drugs These are the main factors on which from the literally enor mous list of anticholinergic drugs available the following selections are given in the order of preference

METHANTHELINE—Doses of 50 to 100 mg of methantheline (Banthine) give moderate to full effects lasting 3 to 6 hours It is also available for parenteral use the recommended dose being 15 to 25 mg intramuscularly, for effects lasting 2 to 4 hours

PROPANTHELINE—Doses of 30 to 45 mg orally of propantheline (Pro-Ban thine) give effects comparable to 50 to 150 mg of methantheline It is also avail able for parenteral use the recommended dosage is 10 to 20 mg

TRIDIHEXETHIDE—The dosage of tridihexethide (Pathilon) is from 25 to 50 mg given orally A parenteral dosage form is also available

A Design for the Use of Anticholinergic Drugs

If these drugs are to be used not as placebos but for their specific pharmaco dynamic effects they must be used in doses sufficient to dry the mouth or produce other minor toxic effects There is no other way of being sure that an adequate dose has been given Because the adequate dose varies with the current intensity of cholinergic stimuli it may be expected to vary from time to time

For these reasons it is desirable to begin continuous therapy with such drugs by using a moderate dose (e g, tincture of belladonna 20 drops or methantheline 50 mg) and to increase the dose stepwise each time the drug is given until minor toxic effects are noted If these are intolerable the dosage level may be set slightly lower but thereafter frequent changes may be required to keep the mouth

physical coating may play a role in their total protective effects against acid it would seem best to judge these compounds on the more readily measurable basis of buffering or neutralizing capacity

With the more absorbable compounds, the true alkalis, antacid effects are usually achieved at the price of some degree of alkalosis and expansion of the extra cellular fluid compartment The alkalosis is due not only to the absorption of cation (usually sodium) from the antacid but also in some instances to the loss of chloride through vomiting Symptoms include anorexia, nausea irritability oc cipital headache muscular aches and tetany In chronic alkalosis with per sistently alkaline urine the solubility of calcium and phosphorus is reduced and phosphatic renal calculi may form In other patients renal function is impaired calcium excretion is depressed and hypercalcemia develops with attendant mani festations of hypertension pruritus, band keratopathy conjunctival crystals, and calcinosis elsewhere (the Burnett syndrome) In more acute alkalosis for which vomiting and antacid use are jointly responsible, paralytic ileus and mental dis turbances are common Especially when hypokalemia is associated, serious and sometimes fatal disturbances of electrical conduction may occur in the heart Be cause of these dangers and because the true alkalis provide only very transient buffering of the gastric juice, their use in the management of peptic ulcer and allied disorders is not recommended

By comparison the dangers inherent in the use of poorly absorbable antacids are quite minor Some of the magnesium compounds (especially MgO) may yield enough absorbable magnesium ion to accumulate in the extracellular fluid and cause cerebral depression This is rarely significant unless renal function is mark edly impaired Magnesium salts are, of course, laxative agents, while calcium and aluminum salts often cause an obstinate constipation These difficulties can usually be overcome by simultaneous use of compounds of both groups Aluminum hydroxide binds phosphate in the intestine in large amounts but depletion of total body phosphorus is easily avoided by feeding 750 mg or more of dietary phos phorus per day—an amount readily exceeded in the usual diets for patients with ulcer

The Several Antacids

Freely Absorbable Antacids—Of the freely absorbable antacids, the only sub stance in common use is sodium bicarbonate For the occasional relief of simple indigestion the powder may be taken in doses of 1 Gm (½ tsp) in half a glass of water Most proprietary preparations for the relief of nonspecific gastric distress add nothing to sodium bicarbonate except color, flavor, and expense The combi nations of sodium bicarbonate with magnesium oxide and with bismuth sub carbonate or calcium carbonate (Sippy powders or tablets) are still widely used in the treatment of peptic ulcer but because of their short duration of action and the attendant dangers of alkalosis they are not recommended

Poorly Absorbable Antacids—The poorly absorbable antacids may be classi fied as follows

Inorganic Salts With Constipating Action —

Aluminum Salts The most satisfactory and most widely used is aluminum hy

THE CHOICE OF AN ANTACID

Introduction

Several kinds of therapeutic agents are widely used for reducing or neutralizing the acidity of gastric juice. This is quite important in the treatment of peptic ulcer, gastritis, hiatus hernia, and pancreatitis, but of little value in other conditions. Their rational use depends upon an understanding of the pattern of secretion of hydrochloric acid in these conditions, and the role of acid in their pathogenesis.

Clinical Applications

In *peptic ulcer, gastritis,* and *peptic esophagitis,* antacids are used for the specific purpose of inactivating pepsin. This is accomplished by buffering the gastric contents to a pH of 4.0 or higher. Actual neutralization is unnecessary, and further it is undesirable, because at pH 7.0 or over the stomach empties more rapidly, sweeps the antacid out of the stomach, and terminates its useful effect. The buffering of acid should be almost continuously effective over days, weeks, or months, and to this end the agent used should be active as long as possible after a single dose, should be palatable and convenient to take, should be free even of inconvenient side effects, and should be relatively inexpensive. For these needs the compounds of aluminum and magnesium are best suited.

In *acute pancreatitis* the buffering of the free acid of the gastric contents serves to diminish the secretion of the pancreas, by reducing the acid stimulus to the secretion mechanism.

The relief of *ordinary indigestion* or epigastric fullness is a trivial but very common application of antacids. This sensation, apparently due to distention of the stomach by swallowed air in the presence of delayed gastric emptying, is well relieved by sodium bicarbonate and other mild alkalis. Their action is apparently twofold—distention of the stomach is first increased by evolution of carbon dioxide, then abruptly decreased by eructation of gas, and alkalinizing the gastric contents hastens its evacuation into the duodenum. As only the occasional relief of this symptom, without removal of the underlying cause can be sanctioned, the use of absorbable alkali is permissible.

General Pharmacologic Considerations

None of these agents interferes with the production of hydrochloric acid, they act only to combine with it, or otherwise modify its effects, after it is formed. The usual mechanism of action is chemical neutralization, which has been amply demonstrated both in vivo and in vitro. For many of the nonabsorbable compounds, in vitro studies indicate a strong capacity to adsorb hydrochloric acid, but the evidence that this is important in vivo is scant. Likewise, many of these agents in colloidal suspension form a tenacious coating, physically very much like mucin, over the surface of a beaker or of the mucosa of the resting stomach. In the presence of copious acid secretion, however, the material flocculates and this physical protection is apparently lost. Without denying the possibility that adsorption and

that the patient be fed hourly when awake and given antacid (e g, 8 to 12 ml of a mixture of aluminum hydroxide and *magnesium hydroxide) one half hour after* each feeding During the first few nights of treatment, the patient should be awakened every 2, 3, or 4 hours for a small feeding (120 ml) of milk and cream alternating with a dose of antacid After this, especially if an anticholinergic drug is given at bedtime (page 356), nocturnal feeding or medication should be given *only* when awake After 2 to 7 days of freedom from pain and active bleeding the patient should be advanced to the '6 feeding" regimen described below

In most patients with gastric ulcer, *hiatus hernia with or without peptic* esophagitis, and pancreatitis, the stomach does not empty so rapidly and its nocturnal secretion is not as large as in duodenal ulcer This permits the immediate adoption of the 6 feeding regimen, in which a well balanced diet is fed in 3 regular meals plus snacks at midmorning, midafternoon, and 1 hour before bedtime Fifteen to twenty milliliters of an antacid mixture is given 60 to 90 minutes after each feeding The timing of the several feedings and doses of antacid is of prime importance In the hospital, whether or not a shortage of nurses exists, the patient himself should help prepare, follow, and record a time schedule, under nursing supervision While at home and at work, responsibility for the schedule may be shared by members of the family and office associates or an interval timer may be used

It should be emphasized that this regimen is designed mainly to control peptic autodigestion and to permit existing ulceration or inflammation to heal That which is most impressive to the patient—the control of pain—is actually incidental and he will usually require strong persuasion to follow this routine for the several additional months after the disappearance of pain which are apparently required for maximum benefit In most cases of duodenal ulcer, for example, which seem not to have been benefited by this regimen, it has been used for only brief periods and antacids have been given only for the relief of ulcer pain

In most cases the full regimen ought to be continued for 2 to 3 months after the control of all relevant symptoms and signs This requires careful inquiry into the daily habits of the patient A taxi driver, for example is more likely to take antacids regularly if they are in tablet form than if they must be poured from a *bottle* In *tapering off ' the therapeutic routine, those doses of antacid* given 1 to 1½ hours after the 3 regular meals should be omitted first then the late morning and late afternoon doses, and finally the bedtime dose Only after 6 months of complete control of symptoms are the interval feedings omitted

Many patients cease to take their antacid because of constipation Though this is not often a problem with the recommended *mixtures of aluminum and magnesium* it is wise not to let any patient become constipated Milk of magnesia (30 to 45 ml) should be added to the bedtime dose of antacid at the outset of treatment and continued each night until it is clear from the results achieved that neither this nor any smaller dose is needed

Rational Basis for New Antacids

The poorly absorbable antacid *mixtures now available* are nearly free of undesirable systemic effects such as alkalosis have little constipating effect, interfere

droxide gel, which is available in liquid or tablet form It has good neutralizing power, some coating and adsorptive activity, and relatively prolonged action The aluminum ion has been shown to inhibit pepsin independently of any changes in pH Aluminum phosphate, basic aluminum carbonate, and dihydroxy aluminum aminoacetate offer no special advantages as gastric antacids

Calcium Salts Precipitated calcium carbonate provides neutralizing power almost as great as that of aluminum hydroxide and is much less expensive Yet because of its disagreeable, chalky taste, and because of less clear evidence of adsorptive or coating actions, it is not to be recommended as highly Other calcium salts are impractical

INORGANIC SALTS WITH LAXATIVE ACTION —These are all salts of magnesium and two are of value

Magnesium Salts Magnesium hydroxide has extremely high neutralizing power and prolonged action in the stomach Magnesium trisilicate has considerably less potency for chemical neutralization but more value as an adsorbent and for its coating properties

ORGANIC MATERIALS —

Anion Exchange Resins The anion exchange resins are efficient adsorbents but weak antacids They cannot produce alkalosis or constipation but they are bulky to use, gritty and somewhat unpleasant to taste, and relatively expensive For these reasons they are little used and are not recommended

Gastric Mucin Gastric mucin, a partially purified alcoholic precipitate prepared from hog stomach, also eliminates the disadvantages of alkalosis, constipation or diarrhea which characterize the inorganic antacids But because of low neutralizing potency, considerable bulk, and disagreeable odor and taste, it is not recommended

Choice of Antacids —For all routine purposes of continued antacid medication, the salts of aluminum and magnesium are recommended Despite a proper disdain for mixtures of drugs, we suggest it is better to give the constipating and laxative agents together, to free the patient from having to plan their alternate use In order of preference (1) aluminum hydroxide with magnesium hydroxide, (2) aluminum hydroxide with magnesium trisilicate

All are available in liquid form (dose, 8 to 30 ml) or as 0 5 Gm tablets (dose, 2 to 8) All tablets should be chewed and thoroughly mixed with saliva before swallowing, with or without small sips of water, to permit prompt and thorough mixing with the gastric contents

A Design for the Use of Antacids

Even with the best of the antacids, the duration of action of a single oral dose is disappointingly short To approach the goal of continuous buffering of gastric acid, they must be administered frequently As dietary protein is also a valuable buffer, the antacid should be taken between the feedings, when the stomach is likely to have emptied itself of food

This is the basis for the well established routines of multiple feedings and interval antacids in the treatment of peptic ulcer In acute and unobstructed denal or marginal ulcer, the extremely rapid emptying of the stomach re

serves rather to distort and hinder the re establishment of normal habits of defecation

When such *chronic use of cathartics* is abruptly suspended, 'withdrawal symptoms appear—bloating, anorexia, headache, giddiness fatigue, and mental depression It is not clear to what extent these are reactions to stress and to what extent they are reflex responses of the irritable intestine to its unevacuated contents In any case, they are relieved promptly by a tap water enema This is known to cleanse only the distal colon, and thus of all the available artificial aids to elimination it most nearly approximates, in its results, a normal bowel movement

Given control of the distressing symptoms, the lasting relief of cathartic addiction depends upon re establishment of the normal reflexes of defecation At the segmental level, mass peristalsis is reinforced by large breakfasts, by ingestion of large amounts of fluid, and by administration of *nonabsorbable hydrophilic colloids*, such as synthetic hemicelluloses and those of psyllium seed and agar These agents increase the bulk and water content of formed stools and render them easier to *pass in the absence of abundant mucus At the suprasegmental level, strong con*ditioning of the defecation reflex is favored by a regular time for breakfast and the toilet visit, a ritualistic program of administration of the colloid material and other measures

Bedridden Patients—It has been pointed out how interruptions in the normal habits of living lead to transient constipation Any illness severe enough to confine the patient to bed or to his home may have this result In most acute illnesses there is reduction in intestinal motility (seen in extreme form in the distention which accompanies pneumonia or heart failure), and a lowered food intake with reduced gastrocolic reflexes The bedpan, aside from its indignity and unfamiliarity obliges the patient to assume a very unfavorable position for defecation The *constipation which usually results unhappily* complicates the patient's distress, is associated with anorexia and depression, and may lead to fecal impaction Efforts to relieve it by straining at stool may result in protrusion of hemorrhoids *worsening of a hiatal hernia, bleeding from esophageal varices, pulmonary* embolism or myocardial infarction Thus its efficient management is highly important

Early in the course of such constipation, *digital examination of the rectum* usually reveals large quantities of soft stool One may infer from this that the main trouble does not lie in reduced intestinal and colonic motility and that only the evacuation of the rectum need be artificially aided *For this the optimum* management is an enema at 1 to 2 day intervals When this is not feasible because of shortage of personnel or for other reasons one should use the mildest cathartic which produces the desired results In order of preference, *this should* be an anthracene derivative, milk of magnesia, or a hydrophilic colloid

Such cathartic administration during a period of acute illness is often the starting point for prolonged habituation to their use The physician *should take* the responsibility of weaning the patient from cathartics during his convalescence

Anal Lesions—In the presence of hemorrhoids, anal ulcers, or other inflamed lesions about the anus, constipation results at least in part from locally induced

only to a slight degree with normal digestion and absorption, and are reasonably palatable and inexpensive Compounds of even greater neutralizing potency are needed, so that more adequate dosage can be given with a reasonable bulk The most valuable improvement, however, would be in a preparation which by and of itself would remain longer in the stomach and would thus reduce or eliminate the need for frequent feedings, as in current regimens

The inherent limitation of antacids is that they act only upon acid already produced, and their dosage is variably adequate, depending upon the level of acid production Current research into the enzymatic mechanisms of the parietal cell, and especially the nearly complete arrest of acid secretion by large parenteral doses of a carbonic anhydrase inhibitor, indicates the future possibility of practical drugs for the control of acid production

THE CHOICE OF A CATHARTIC

Introduction

Drugs have been used since time immemorial for the purpose of promoting defecation Such agents are widely self administered by lay persons Whatever the psychological basis there is a durable attitude spanning many centuries and many cultures that associates excrement with evil and its elimination with the expiation of guilt The practical result is that most people in our society still regard even transitory constipation as something to be directly and promptly treated with a cathartic In the past the medical profession has abetted these tendencies by the empiric and nonspecific use of purgation in the treatment of systemic disease (even of the common cold) and has been slow to disown the theory of intestinal autointoxication As a consequence, more patients now consult the physician because of the untoward effects of chronic use of cathartics than for any condition that can be relieved by them

Much of the following discussion, therefore concerns the temporary use of some cathartic agents as a means of weaning the patient from cathartic addiction The remainder deals with the relatively limited conditions under which a cathartic should be prescribed de novo In any of these situations in which the physician administers a cathartic he is obligated to have just as when he gives a narcotic agent some plan as to how the need for the drug can and will be terminated

Clinical Applications

Cathartic Addiction —The most common cause of chronic constipation, as a presenting complaint in office or clinic practice, is the habitual use of cathartics This arises in most instances because the patient has an unduly rigid concept of the need for regular elimination which leads him to resort to laxatives for quite transient constipation His use of increasingly potent drugs in the attempt to restore regular and predictable bowel movements leads to persistent overstimulation and irritability of the intestines While the average spontaneous bowel movement empties only the rectum, sigmoid and perhaps the descending colon, that produced by a cathartic may include part or all of the fluid content of the proximal colon and even of the lower ileum As a result the self-administration of cathartics, undertaken to ensure regularity of bowel movements, rarely accomplishes this and

tion is being corrected In some of the milder cases of Hirschsprung's disease the extra stimulation afforded by them to the dilated, normally innervated proximal segment of the colon may assist it to force stool past the narrowed distal segment The use of urecholine or methacholine and of enemas of physiologic saline is however, more widely practiced In all of these situations the milder agents such as milk of magnesia or cascara sagrada should be used, and more drastic cathartics will not be justified by their results

General Pharmacologic Considerations

Basis of Action of Cathartics —The general level of intestinal propulsive activity is the product of the irritability of the bowel and the stimulus provided by its luminal contents Most cathartics act either by increasing the volume of the luminal contents or by increasing the irritability

1 Many useful agents act by *increasing the water content* and hence the bulk, of chyme and feces These mechanisms are

a Osmotic, as in the common saline cathartic, *in milder inorganic agents* such as milk of magnesia, and in a number of natural foods with cathartic properties Thus fruits and fruit juices are laxative, at least in part because of the osmotic activity of their sugars and organic acids The effect of such agents is most marked in the upper small intestine, where the increased volume of contents sets up peristaltic rushes and ultimately reduces the time available for dehydration of the fecal mass in the colon

b Hydrophilic activity of certain colloids, which increase the volume of the gastric and jejunal bolus if large quantities of water are given simultaneously, and which oppose the normal dehydration of the fecal mass thus tending to increase its size

c In comparison with these two mechanisms, it is probable that directly increasing the ingested volume of water or food roughage has only minor significance as a cathartic measure

2 The *irritability* of the intestines can be increased by a variety of systemically acting drugs such as neostigmine, methacholine, and pituitary vasopressin which are not generally considered as cathartics and are discussed elsewhere Many common cathartics act, however, by so irritating the intestinal mucosa that propulsive motor responses to normal or even reduced luminal contents are potentiated The site of action of these irritants varies—with the stronger ones such as castor oil and phenolphthalein the small and large bowel are both acted upon the milder anthracene derivatives seem to irritate only the colon

3 Another mechanism of action, of value in some clinical situations *is that* of *lubrication* of the anal canal to permit the easier passage of formed stools With agents taken orally, this is a property only of chemically inert substances such as mineral oil and the cellulose derivatives

THE ENEMA —Enemas act both by increasing the fluid bulk of the colonic contents and in some instances by irritating the mucosa Retention enemas serve to soften and lubricate *the feces easing the passage of* extremely hard stools Thus all of the mechanisms of action of the useful cathartics are involved in the actions of enemas

reflex spasm of the anal sphincter Since retention of feces is followed by the necessity of passing hard fecal masses which abrade or further irritate the inflamed structures, it is important to keep the bowels moving On the other hand, too vigorous catharsis leads to an increase in the total amount of straining at stool and to the embedding of small amounts of semiliquid feces in crypts, ulcers, and fistulous tracts What is desired is a single, formed, well lubricated, easily passed stool each day This is achieved, in conjunction with efforts to diminish sphincter spasm by hot sitz baths and local anesthetic agents, by the use of mineral oil or the hydrophilic colloids While reasonable theoretical objections have been raised to the use of mineral oil on the grounds of interference with fat absorption and the possibility of setting up a granulomatous process in the inflamed tissue, in practice these do not seem significant when it is properly used Accordingly, mineral oil is recommended as empirically superior in producing an easy bowel movement

Purging.—Today there remain only a relatively few indications for purging the intestines

Preparation for Examination.—In preparation for abdominal x rays particularly for pyelography and for barium enema, the elimination of gas shadows is desirable For a barium enema the colon must be emptied almost perfectly of all its contents Since saline cathartics are likely to leave behind gas and fluid residues, irritant cathartics are preferred Empirically castor oil has proved most effective, but senna powder is often a satisfactory substitute, especially for pyelography In preparation for sigmoidoscopy purging and enemas may be used together

Hepatic Coma.—The major source of ammonia in the body is the large intestine, where bacteria produce it by acting upon products of digestion of proteins In hepatic coma and precoma the ammonia level in the blood may be reduced not only by lowering of the protein intake and administration of broad spectrum antibiotics, but also by purging and enemas Saturated solution of sodium sulfate is recommended, to be used each morning for 1 to 3 days

Elimination of Poisons.—Some poisons, especially the heavy metals such as mercury, are excreted by the lower bowel and passed in the stool This process may be accelerated, and the damage to the intestinal mucosa apparently diminished, by purging Again a saline cathartic such as sodium sulfate is most useful

In Conjunction With Anthelmintic Agents.—Many of the widely used acutely acting anthelmintics, such as tetrachlorethylene, oil of chenopodium, and oleoresin of aspidium, are held to require preliminary purging of the bowel to ensure contact of worm with drug in concentrated form and further purging during or after treatment in order to prevent undue absorption of the toxic anthelmintic drug For these purposes sodium sulfate is recommended

Examination of Stools for Parasites.—In the microscopic examination of the stools for amebae, other protozoa, and larvae of some worms, a fresh liquid stool is needed for maximum efficiency of examination A rapid acting agent is required, and to avoid oily residues it must be a saline Sodium sulfate is again the agent of choice

Miscellaneous.—In lead poisoning, hypothyroidism, and hyperparathyroidism, laxatives may be temporarily needed while the underlying cause of constipa-

catharsis may lead to persistent weakness, anorexia, and lethargy at least partly attributable to depletion of extracellular water and potassium

HABITUATION —The most common untoward effect of cathartics is habituation to their use In many patients this is the result of prolonged self administration due to complex neurotic patterns and familial misinformation In others, as indicated previously this hazard can be avoided when the physician assumes the same degree of responsibility for discontinuing cathartics as he does for prescribing them

The Several Cathartic Drugs

The most useful cathartics may be classified as follows

Those Increasing the Bulk (Mainly the Water Content) of the Stools —

OSMOTICALLY ACTIVE AGENTS, THE SALINE CATHARTICS —

Those With Vigorous Action, the Saline Purge The magnesium salts (magnesium sulfate and magnesium citrate) are not recommended for repeated use because of the danger of absorption of significant quantities of magnesium ion, with consequent cerebral depression *Sodium sulfate* is efficient, chemically nontoxic and inexpensive A dose of 15 Gm is given, usually as the saturated (approximately 50 per cent) solution Its only disadvantage is its bad taste, which can be overcome by substitution of *sodium phosphate* (5 to 10 Gm), or *effervescent sodium phosphate* (10 Gm)

Those With Milder Action The only important preparation of this class is *milk of magnesia,* an aqueous suspension of magnesium hydroxide, 15 to 45 ml gives mild laxative action

THE HYDROPHILIC COLLOIDS —A wide variety of these agents are derived from agar gums (tragacanth karaya, bassora), psyllium seeds, and other natural sources as well as synthetic cellulose derivatives None has serious toxic effects, and their potency as laxative agents does not differ greatly from one to the other The choice can thus be based upon considerations of palatability, convenience, expense and suitability for the ritual needs described on page 368 Accordingly, the following are recommended

Psyllium Hydrophilic Mucilloid With Dextrose This material (Metamucil) is a highly purified psyllium preparation, to be taken as 1 to 2 teaspoonfuls stirred in a whole glass of water, and swallowed within 30 seconds

Serutan This consists of the husks of psyllium seed (55 per cent) with dextrose and is taken in the same manner as Metamucil

Agents Lubricating the Stools for Easy Passage —Here the only material of importance is *mineral oil* (liquid petrolatum) It may be light' or heavy, and cheap grades, if of U S P standard, are fully satisfactory A dose of 15 to 45 ml is taken at bedtime Flavored and emulsified preparations are more expensive and their only advantage is greater palatability A common emulsion also contains phenolphthalein, and this should be avoided when only lubricating action is desired

Agents Producing Catharsis by Irritation —

STRONG IRRITANTS —The most widely used agent of this type is *castor oil* recommended as a purge in doses of 30 to 60 ml, given in the manner outlined on

An enema properly administered comes closer than any cathartic to imitating a normal bowel movement in the sense that only the rectum sigmoid and part or all of the descending colon is evacuated If the enema fluid is to reach the sigmoid level or higher the spastic contractions of the rectosigmoid area must be prevented or overcome For this reason enemas should be administered at or just above body temperature with the patient *lying down* in a comfortable position (not sitting on the toilet) and at a pressure not exceeding 60 cm (24 inches) of water When an urge to defecate is experienced one may be sure the enema fluid is distending the rectum if the tube is then clamped or the flow otherwise interrupted the sensation will soon subside as the fluid passes upward into the sigmoid Patience with the interruption and resumptions of the procedure in this manner even several times in succession and occupying 10 to 15 minutes if necessary is a prerequisite to good results Further details of procedure are given in the consideration of the several types of enemas in the following section

Therapeutic Effects —The desired therapeutic effects of cathartics are generally either the purging of the intestinal tract or the stimulation of a normal daily bowel movement The results depend not only upon the agent used and the dose thereof but also on the state of activity of the gut at the time it is given Thus the speed and efficiency of action of castor oil is greatly enhanced if it is given on an empty stomach and larger doses of any laxative are required for a given result in a bedridden patient or a patient receiving other drugs such as opiates or aluminum hydroxide which have a constipating effect

Dangers —The use of cathartics in any form carries with it certain risks most of which happily can be foreseen by the prudent physician

Inflammatory Disease —Inflammatory disease of the intestine and adjacent organs is often dangerously complicated by the intestinal hypermotility induced by a cathartic The use of such an agent in acute appendicitis has undoubtedly led to perforation and peritonitis on numerous occasions and equally devastating consequences have occurred in diverticulitis regional enteritis ulcerative colitis, and other inflammatory conditions *Abdominal pain of uncertain origin is a contraindication to the use of a cathartic*

Intestinal Obstruction —Intestinal obstruction if present, is certainly aggravated by cathartics and may be precipitated by them de novo With incomplete obstruction where only a narrow lumen is left by an encircling inflammatory or neoplastic process the lumen is likely to be obliterated when engorgement of the mucous membrane is provoked by the cathartic Obstruction has also been caused chiefly in the lower esophagus when hydrophilic colloid laxatives have been taken with less than the prescribed amounts of water *In x ray studies of patients with symptoms of obstruction the barium enema should be performed first without the customary preparation with castor oil*

Fluid and Electrolyte Loss —The fluid contents of the ileum and proximal colon are rich in Na^+ K^+ Cl^- and HCO_3^- When a patient is suddenly and drastically purged dehydration hypokalemia and acidosis or alkalosis may result While young and otherwise healthy persons may quickly recover from this insult aged individuals and those with renal disease sometimes suffer acute renal failure cerebral infarction or other unhappy consequences The chronic use of vigorous

RETENTION ENEMAS —These enemas are used to soften or lubricate hard impacted fecal masses Cottonseed oil is ordinarily used 150 to 180 ml being slowly introduced and retained for several hours Recently superior results have been achieved with dioctyl sodium sulfosuccinate (Colace) in 1 per cent solution 5 ml of which is diluted in 60 to 90 ml of water for use as a retention enema Either procedure should be followed by an evacuant enema of tap water, saline or soap suds

A Design for the Use of Cathartics

Relief of Cathartic Addiction —To accomplish this the mildest possible cathartic should be used as a temporary aid and to a large degree as a placebo in a program which also includes the re establishment of regular visits to the toilet a regulated diet and other ritualistic measures designed to promote defecation as a conditioned reflex The care with which the hydrophilic colloids must be taken becomes part of this ritual Thus one rounded teaspoonful of Metamucil or Serutan is stirred briskly into suspension in a full glass of cold water, drunk within 30 seconds then followed by another full glass of water This procedure is followed at bedtime and again immediately on arising

This regimen is expected to restore regular daily bowel movements only after 1 to 4 weeks and the patient is so informed 'Withdrawal symptoms are relieved by a tap water or phosphate enema administered at 2 to 7 day intervals in the morning immediately after the regular toilet visit The patient is encouraged to widen the interval between enemas as rapidly as possible and to take the enema only for the relief of severe symptoms

After 4 to 6 weeks of such therapy, the colloid laxative can usually be discontinued It can be used again prophylactically whenever changes in the routine of living (travel, intercurrent infection) might lead to transient constipation but it should be emphasized to the patient that he has no permanent need of this or any other cathartic agent

It should be emphasized that the same general regimen is often successful when *all* laxatives are omitted at the start The use of the hydrophilic colloid is recommended here mainly as a placebo

Bedridden Patients —In bedridden patients the use of cathartics should be a supplement to or a reluctantly accepted alternative for, other measures which deal more rationally with their constipation

1 *Encourage a regular effort* at defecation daily after breakfast

2 *Banish the bedpan* In the vast majority of bedridden patients the pan can be safely and efficiently placed in a bedside chair, or, better replaced by the commode Whenever the patient can sit up to defecate and can use more familiar facilities constipation is less serious Many sensitive persons find it impossible to defecate when others are in the room—hence a transfer to a single room and the temporary absence during defecation of nurses and other attendants are desirable

3 *Omit constipating medication* if possible Do not use morphine or codeine for pain if Demerol or aspirin will do Minimize the use of constipating antacid

page 369 Other irritants commonly used are either too strong (e g, croton oil), or too often associated with systemic intoxication (as in the case of podophyllum or phenolphthalein)

IRRITANT CATHARTICS OF INTERMEDIATE STRENGTH —A useful member of this group is *compound powder of senna*, in which the laxative action of senna is combined with the demulcent and flavoring qualities of glycyrrhiza If it is to be used as a purge in preparation for abdominal x-rays, 10 Gm must be taken in the same manner as indicated for castor oil

MILDLY IRRITANT CATHARTICS —A useful cathartic of this type belonging to the emodin or anthracene group is *cascara sagrada fluidextract*, of which 2 to 6 ml may be taken at bedtime with expectation of a soft or semiliquid stool the following morning Its action is believed to be confined to the large intestine, but apparently the entire colon, rather than just the distal colon, is affected The only notable toxic reaction which follows its chronic use, is the symptomless development of a diffuse, blotchy, brownish black pigmentation of the entire colonic mucosa, known as *melanosis coli* This apparently has no clinical significance

Other cathartics of the anthracene group are less satisfactory—rhubarb because of secondary constipating effect, and aloin because of griping

Enemas —Of the many kinds of enemas, the following are recommended as most generally useful

THE TAP WATER ENEMA —Tap water (500 to 1,500 ml) at body temperature or slightly higher, is the most satisfactory enema fluid when irritation must be scrupulously avoided, as in diverticulitis, ulcerative colitis, or other inflammatory conditions It is contraindicated in infants with congenital megacolon, in which it is retained so long that considerable quantities of water are absorbed and the electrolytes of extracellular fluid become dangerously diluted This can be avoided by substituting physiologic saline for tap water

THE HYPERTONIC ENEMA —Saturated solution of sodium phosphate, 120 ml when given per rectum causes the rapid distention of the left colon as it attracts fluid osmotically into the lumen of the bowel The resulting evacuation occurs without griping, but a moderate irritation of the mucosa is produced This solution is available in disposable plastic containers at small cost and saves hours of time of nurses and attendants when substituted for tap water and soap suds enemas It is also an excellent preparation for proctoscopy It can be recommended in all patients except those with colitis or diverticulitis Of the several manufactured preparations, the only difference is in the convenience of the plastic container Recommended, in order, are Travad Enema, Clyserol, and Fleet Enema Similar advantages can apparently be obtained with a prepared enema formulation (the Sigmol enema), which contains in 120 ml Sorbitol solution, 45 Gm, and the wetting agent dioctyl potassium sulfosuccinate, 0 12 Gm This material is considered to have less irritant action upon the colonic mucosa than does sodium phosphate, and to eliminate the risk of absorption of large quantities of sodium

SOAPSUDS ENEMA —The procedure is the same as for tap water enema, except that white toilet soap is stirred in the water until it is moderately opalescent This is contraindicated in ulcerative colitis, diverticulitis, and other severe inflammatory disease of the colon

For all other situations in which purging is required, the use of sodium sulfate 45 to 60 ml of saturated (50 per cent) solution, is recommended This should be given in the morning on an empty stomach and followed by 2 or more glasses of iced water, citrus fruit juice, or ginger ale When, as in treatment of poisoning or hepatic coma repetitive dosage is required, succeeding doses may be given as soon as the effects of the earlier dose are obtained The volume of the stools should be measured in such cases and the calculated losses of fluid and electrolytes should be replaced

Rational Basis for New Cathartic Agents

The ideal cathartic, that which would most closely simulate the natural mechanism of defecation would act on no portion of the bowel other than the distal colon There, without irritating the colonic mucosa, it would suddenly stimulate expulsive movements confined to this area, 10 to 30 minutes after breakfast The action of an ingested drug could be confined to the distal colon if it were completely nonabsorbable, chemically activated by contact with the digestive juices and then active on reaching a critical concentration as the feces is dehydrated Until such a remarkable drug is made available, the nearest substitute will be an enema

Bisacodyl (Dulcolax) is a promising laxative agent only recently released in the United States It is said to cause evacuation by inducing reflex propulsive motility of the colon on contact with its mucosa Evidence indicates that irritation of the mucosa is minimal to absent, and that the bowel is emptied without purging the resulting stools being soft to formed in character Emptying of the colon is so complete that this agent provides a very satisfactory preparation for barium enema or proctoscopy It is effective 8 to 10 hours after oral ingestion and within an hour after insertion of a suppository It is available as 5 mg tablets and in suppositories containing 10 mg Recommended dosage is 15 mg orally at bedtime If used as preparation for barium enema or proctoscopy, a suppository should be inserted 1 hour before the procedure

THE CHOICE OF AN ANTIDIARRHEAL AGENT

Introduction

Antidiarrheal medications are less widely used than cathartics in the United States because diarrhea is less common a problem in temperate climates than is constipation In addition, agents directed against diarrhea are more likely to be used under medical supervision because of the urgency of the symptom and the physiologic consequences of the severe or prolonged diarrheal state There is nothing so disruptive of normal social and business functions as the recurrent threat of an urgent bowel movement In general we have adequate drugs to deal with the acute diarrheal states but are sorely limited in the safe usage of drugs for the chronic diarrheas Our limited knowledge of the basic physiologic mechanisms of diarrhea has prevented specifically directed pharmacologic therapy We are compelled on the one hand, to employ powerful and effective agents that have deleterious extraintestinal effects and are habit forming or on the other hand to

agents (containing calcium or aluminum) or balance these with magnesium salts The potent anticholinergic drugs and the ganglionic blocking agents may cause obstinate constipation

4 *Get rid of barium sulfate residues* These are very likely to become inspissated in the distal colon, especially when the barium has been given by mouth for gastrointestinal series or for outlining the left atrium They are efficiently removed by an oil retention enema, followed by a soapsuds enema, but a saline purge or anthracene cathartic may be substituted

5 *Give an enema,* as soon as his condition permits, to any patient who has failed to have a bowel movement in the preceding 3 days

In the less prostrate patients, these measures should be adequate to promote fairly regular bowel movements If, however, movements are small and hard or if none is produced for 2 days, 6 ml of fluid extract of cascara alone, or in combination with 30 ml of milk of magnesia, is given at bedtime 2 out of every 3 nights If the bowels move on the mornings after no medication is given, the cathartic may be omitted or replaced by Serutan, Metamucil, or mineral oil given in the manner previously indicated

In more severely ill patients, it is wise at first to minimize their effort in getting on and off the bedpan and in straining at stool, by using only enemas of tap water, of hypertonic phosphate solution, or of soapsuds every 2 or 3 days after breakfast As they improve, it would be wise to resort at once to cascara and milk of magnesia 2 nights out of 3 without waiting to see whether they can cause their bowels to move spontaneously

As soon as any previously bedridden patient is allowed to be up, his cathartics should gradually be eliminated and his toilet habits re-established, in the manner outlined for "cathartic addicts"

Anal Lesions—In the presence of painful anal lesions, the passage of a daily stool may be best aided by mineral oil This is always given at bedtime, to avoid its mixing with food, in the amount of 30 ml If this is insufficient, after 2 days, to be detectable on the toilet paper or as brown stained drops on the water of the toilet bowl, the dose is increased to 45 or even 60 ml When this "leakage" is observed, the dose is reduced by 5 or 10 ml and then maintained at this level for 3 to 4 weeks after the disappearance of pain, bleeding, and other local symptoms In this manner a maximum of lubrication is achieved without leakage, and the mineral oil is used for too short a period to incur chronic untoward effects

Purging—The complete cleansing of the lower bowel called for in abdominal x rays is best accomplished with castor oil, 45 to 60 ml, given in a single dose on an empty stomach in the late afternoon preceding the day of examination It should be well disguised by some flavoring agent such as raspberry syrup, additionally sweetened, and mixed with cold carbonated water to a total volume of over 200 ml The purpose of all this, which is readily accomplished by the local pharmacist, is to overcome nausea and thus ensure its rapid passage through the stomach and its abrupt irritant effect upon the intestine It may be followed after 2 hours by a light supper, and the most vigorous catharsis is likely to be over by bedtime (The giving of castor oil at bedtime, on the other hand, practically ensures an uncomfortable night)

helpful in reducing night diarrhea when taken in large doses at bedtime The patient with regional enteritis particularly terminal ileitis may be, however, in a state of compensated, incomplete intestinal obstruction, that is, proximal intestinal hypertrophy permits flow of small bowel contents through a cicatrized lumen Care must be taken not to produce a decompensation of this state by anticholinergic therapy In the presence of abdominal distention, bowel sounds characteristic of incomplete obstruction or radiologic evidence of dilated loops of small bowel this group of drugs should not be used in regional enteritis In severe, fulminating ulcerative colitis, paralytic ileus may be precipitated by anticholinergic therapy Such therapy is contraindicated in the patient with ulcerative colitis who is more than mildly distended or who has radiologic evidence of large bowel dilatation

Opiates should not be used in this group of chronic diseases except under the following circumstances (1) in cases of diarrhea of such severity and duration as *to threaten physical exhaustion when all other measures including steroid therapy* have failed and (2) when the physician is seeing for the first time a patient who is markedly discouraged and depressed by his illness to put an abrupt end to the diarrhea and thus gain the *patient s respect and confidence* as a basis for subsequent superficial psychotherapy Under the latter circumstances it is usually wise to use steroid therapy concurrently, provided there are no contraindications In either case the patient should be weaned gradually from opiates as soon as possible certainly within 2 to 4 weeks

Malabsorption Syndrome (Sprue, Lymphoma, Whipple's Disease).—More or less specific therapy is presently available for these disorders, and the nonspecific antidiarrheal agents are rarely if ever indicated except when the patient with lymphoma has become resistant to such therapy

Acute Infectious Diarrheas (Viral, Staphylococcal, Salmonella, Shigella)—These conditions are self limiting and of short duration One should not hesitate to use opiates liberally under these circumstances in order to ensure patient comfort Simultaneous replacement of fluids and electrolytes, especially in infants must be undertaken

Chronic Infectious Diarrheas (Amebiasis)—Specific therapy is indicated in amebiasis, and rarely the temporary use of opiates may be necessary until specific therapy becomes effective

Postvagotomy and Postgastrectomy Diarrhea—In view of the increased incidence of chronic salmonella *infection in the postgastrectomy state*, appropriate bac*teriologic studies of the stool* are indicated whenever diarrhea appears following resectional surgery of the stomach In the absence of such specific etiology, the treatment of this group of diarrheas is usually limited to avoidance of (1) ice cold liquids and (2) large amounts of fruits and vegetables Occasionally pancreatic extract in proper amounts may diminish the diarrhea of the postgastrectomy state There is no evidence that a diet low in carbohydrate will relieve this type of diarrhea although it often will relieve other symptoms of the dumping syndrome

Postantibiotic Diarrheas and Pseudomembranous Enterocolitis—If *Staphylococcus aureus* can be cultured from the stool appropriate antibiotic therapy can be based upon sensitivity studies of the organism When this information is not available in patients with severe diarrhea *following extensive abdominal surgery* or

use more benign but much less effective medications that much too often prove inadequate for control of the diarrhea

Clinical Applications

Irritable Colon (Mucous Colitis, Functional Diarrhea)—This condition may perhaps be more properly termed "irritable small intestine and colon," yet the part (if any) played by the small bowel has not been well defined Increased peristaltic activity of the large bowel occurs with the passage of frequent stools of increased water content and usually accompanied by varying amounts of mucus This state is often associated with nervous tension, and it may be that such tension in some susceptible patients leads to excessive neurogenic bombardment of the colon, resulting in increased peristaltic activity and increased mucus formation The consequent decreased passage time through the water absorbing proximal colon is felt to be the basis for the liquid character of the stool Other hypotheses, however, cannot be denied These include the concept of a primary colonic defect in water absorption resulting in frequent 'built in' enemas and the idea of dysfunction of the small bowel with secretion (or failure of absorption) of a specific irritant to the colon (perhaps a fatty acid)

Adsorbents, mucosal astringents, and *hydrophilic substances* are often used in combination as well as separately They have the virtues of being relatively inexpensive and practically free of toxicity However, it is doubtful whether their usefulness in the irritable colon extends beyond a placebo action If the symptoms are mild and infrequent such placebo action may be sufficient to give the patient relief

Anticholinergic drugs are uniformly effective in reducing peristaltic activity in the normal colon and may be effective in the abnormally stimulated irritable colon if properly used The dosage must be pushed to bearable toxicity" and untoward effects anticipated (see page 356) Together with other measures such as environmental manipulation psychotherapy, and dietary restrictions, properly administered anticholinergic therapy often proves helpful It has the great advantage of not being habit forming

The *opiates* are powerful and reliable inhibitors of propulsive activity of the bowel If used in sufficient dosage, one or the other of the opiates can almost always stop the diarrhea of the irritable colon However, in view of their addictive properties they should be used in this chronic disease only rarely In initiating a therapeutic regimen with a patient who has suffered from the irritable colon with diarrhea for an extended period and in whom the disease has proved incapacitating, the physician may use an opiate for a short period in order to gain the patient's confidence and establish a basis for a subsequent psychotherapeutic approach

Chronic Inflammatory Diseases of the Intestines (Ulcerative Colitis, Regional Enteritis)—*Adsorbents, mucosal astringents,* and *hydrophilic agents* are of no use in this group of diseases

The *anticholinergic drugs* are occasionally helpful in diminishing the diarrhea of chronic inflammatory diseases of the intestines These drugs are particularly

HYDROPHILICS —These substances may occasionally impart adhesiveness to a watery stool, but do not diminish the frequency of diarrhea The dosage of the two following products is 1 to 2 *teaspoonfuls in a full glass of water, twice daily* (1) psyllium hydrophilic mucilloid with dextrose (Metamucil) and (2) Serutan, husks of psyllium seed with dextrose

The Anticholinergic Drugs —See page 354

The Opiates —In the patient who can take oral medication the preparations of choice are deodorized opium tincture, camphorated opium tincture (paregoric), and codeine (sulfate or phosphate) When parenteral medication is required, morphine sulfate is the drug of choice

DEODORIZED OPIUM TINCTURE —This is a 10 per cent solution of powdered opium the average adult dose of which is 0 6 to 1 5 ml, 2 to 4 times daily It is ordinarily given as 8 to 20 drops in a small amount of liquid such as water This medication is an effective constipating agent and has the advantage of great flexibility of dose inasmuch as it can be conveniently measured in drops

CAMPHORATED OPIUM TINCTURE (PAREGORIC) —This is a 4 per cent solution of opium tincture containing a number of inactive ingredients which impart to the *solution a characteristic odor and taste The average adult dose is 4 to 8 ml given* 4 to 6 times daily This preparation has no real advantage over deodorized opium tincture

CODEINE —This may be treated as pharmacologically weakened morphine The usual adult dose is 16 to 64 mg, 2 to 4 times daily Codeine has two distinct advantages in the treatment of the chronic diarrheal state First, it is less addictive than opium because it does not induce the equivalent degree of euphoria However, it is false to assume that it may never cause addiction Second, its nondescript appearance may permit the physician to dispense the drug without informing the patient of its name or nature This diminishes psychologic addition to the drug

MORPHINE —In doses of 8 to 20 mg by the parenteral route this drug is useful in the symptomatic treatment of exhausting, acute, diarrheal states It should never be used in the chronic diarrheal states for fear of addiction

A Design for the Use of Antidiarrheal Agents

Therapy of the diarrheal state should be directed toward the etiologic agent if possible This is readily accomplished in some of the infectious diarrheas for which we have specific antimicrobial agents Under such circumstances, the most powerful nonspecific antidiarrheal agent available (opiates) should be employed in the acute stages before specific therapy becomes effective, provided the patient manifests enough discomfort The self-limiting diarrheas permit the same freedom of action with the opiate group of drugs In the care of the chronic diarrhea of unknown or poorly defined cause, however, all efforts should be made to control the diarrhea without recourse to opiates If the patient's exhausted physical state justifies the use of opiates, the smallest dosage compatible with reasonable comfort should be employed If at all possible, the patient should not be acquainted with the name or dose of opiate used

In general, reliance should be placed on more physiologically oriented therapy

the use of broad spectrum antibiotics treatment should be begun at once with novobiocin 0.5 Gm 4 times daily or the combination of erythromycin 0.5 Gm 4 times daily and chloramphenicol 1 Gm 4 times daily and continued for 7 days Any antibiotic which the patient had been receiving when the diarrhea began should of course be discontinued The cultured milks (buttermilk yoghurt) and the lactobacillus preparations appear to be ineffective in these patients

General Pharmacologic Considerations

Adsorbents, Mucosal Astringents, and Hydrophilic Agents.—These substances are said to absorb intestinal irritants physically (absorbents) to diminish mucus secretion and transudation of fluids by precipitation of both mucus and the cell membranes of the surface epithelium and thus to provide a barrier to bowel irritants that may be present within the lumen (astringents) and to reduce the free water content of the stool by incorporating the water and producing a gelatinous mass (hydrophilics) Since none of these mechanisms is specifically directed against the postulated motor mechanism of hyperperistalsis it is not surprising that these drugs are relatively ineffective as antidiarrheal agents

These substances are virtually free of toxicity The amounts taken are limited by the benign dyspepsia they induce The hydrophilic substances should be taken with large amounts of water in order to prevent esophageal obstruction

Anticholinergic Drugs.—See page 353

Opiates.—These drugs have a powerful constipating effect by virtue of their action on the smooth muscle of the colon Opiates cause a marked increase in nonperistaltic activity and a corresponding reduction in peristaltic activity This effect is partially antagonized by atropine Inasmuch as all diarrheal states—whatever the diverse ultimate causes may be—are mediated through increased peristaltic activity of the colon opiates are effective in all such states

The great deficiency of this very effective antidiarrheal group of drugs is addiction and tolerance The threat of addiction is so great that one should hesitate to use the opium derivatives in the chronic diarrheal states except for the limited indications listed above and then for as short a period of time as possible No such cautions are necessary in using opiates in the acute self limiting diarrheal states Other untoward effects of the opiates include occasional precipitation of biliary colic and acute pancreatitis as a result of induced spasm of the sphincter of Oddi The parenteral administration of the opium derivates to asthmatics should be given if at all only with extreme caution The depressed state of consciousness induced by opiates has to be considered in treating the ambulatory patient

The Several Antidiarrheal Drugs

The Adsorbents Mucosal Astringents, and Hydrophilic Agents.—These are of limited value and probably exercise a therapeutic effect largely by virtue of suggestion Choice of a particular preparation should be guided by palatability and price

Adsorbents and Astringents.—The dosage of the 2 listed products is 15 to 30 ml 4 times daily (1) kaolin with pectin (Kaopectate) and (2) aluminum hydroxide

by virtue of the general air of well being induced or by stimulation to t secretion, is not known

Digestants such as hydrochloric acid, pepsin, pancreatic extracts and bil and acids have *no value in this condition* beyond a placebo effect However cannot deny that the placebo effect may be quite potent in the hands of c practitioners, and the use of these medications for functional dyspepsia is ind under such circumstances

Pancreatic Deficiency—Large doses of a potent pancreatic extract ar tremely efficient in the treatment of the steatorrhea and creatorrhea, diarrhea malnutrition of chronic pancreatic insufficiency, such as may be seen in ch pancreatitis

General Pharmacologic Considerations

Cholinergic Drugs—Those gastrointestinal disease states marked by hypo tion would seem to be susceptible to therapy with drugs that stimulate cholin receptors, inasmuch as cholinergic activity increases the functional activity o gastrointestinal tract However, as with anticholinergics, the cholinergic c available have no differential organ activity Apart from the treatment of postop tive abdominal distention and postvagotomy gastric atony, hypoactive states o gastrointestinal tract cannot be ameliorated without courting distressing and gerous side effects The latter include coronary vasoconstriction bronchosp and excessive sweating This group of drugs is dangerous in the presenc asthma, chronic lung disease, and coronary artery disease

Digestants—It would be reasonable to provide available digestants as su tution therapy if it could be shown that deficiency of such digestants gave ris disease states Of all the digestants available, the deficiency of only two— exocrine secretion of the pancreas and bile salts and acids—have been prove give rise to significant symptoms Achylia gastrica may give rise to pernic anemia, but only by virtue of the absence of intrinsic factor, and not becaus the deficiency of pepsin or hydrochloric acid Pancreatic deficiency, on the ot hand, gives rise to clear cut and distressing symptoms, which can be promptly rected by *adequate* (page 377) amounts of commercial pancreatic extract In instances of chronic biliary obstruction, steatorrhea or constipation may res It is felt that the steatorrhea is due to the absence of bile salts in the gastrointe nal lumen In some instances of incomplete biliary obstruction constipation said to be related to bile acid and salt deficiency Substitution therapy is not vised however, inasmuch as oral ingestion of bile acids would aggravate pruritis from which these patients usually suffer Wetting agents are very effect in the treatment of this rare kind of constipation

The Several Stimulant and Digestant Agents

The Cholinergic Drugs.—

NEOSTIGMINE (PROSTIGMIN)—The usual parenteral (subcutaneous or int m scular) dose in the treatment of postoperative abdominal distention is 0 25

(e g, steroids in ulcerative colitis) on the use of placebo therapy if possible (Kaopectate in mild infrequent attacks of mucous colitis), or on the anticholinergic drugs The latter often require dosage sufficient to induce minor toxicity (as outlined on page 353) Proper respect in this case must be paid potential un toward reactions described earlier (page 354)

Rational Basis for New Antidiarrheal Agents

A normal bowel pattern is an integrated bodily activity toward which physio logic phenomena occurring in all parts of the body contribute The controlling center is in the central nervous system The ideal antidiarrheal drug would have its site of action centrally at the integrating center In the absence of such a dream drug an agent inhibiting peristaltic activity peripherally (such as mor phine) and lacking undesirable side effects (such as addiction) would seem a wel come addition to our antidiarrheal armamentarium

THE CHOICE OF STIMULANTS AND DIGESTANTS

Introduction

The diagnosis of suboptimal function of the processes of digestion continues to be a favorite one among physicians It is also a popular self diagnosis among pa tients Therefore it is not surprising that the prescription of gastrointestinal stimu lants and digestants particularly the latter constitutes a major segment of office therapy today Unfortunately w th a few notable exceptions the clinical efficacy of this group of drugs is open to much question

Clinical Applications

Postoperative Distention, Including Postvagotomy Gastric Atony —The cholin ergic drugs neostigmine (Prostigmin) bethanechol (Urecholine) and methacholine (Mecholyl) are useful in postoperative abdominal distention Neostigmine is more useful in the early postoperative period when parenteral medication is necessary Urecholine may be given orally and is therefore used later in the postoperative course Because of its unpleasant side effects Mecholyl a potent parenteral drug is ordinarily not used unless Prostigmin proves ineffective In the case of post vagotomy gastric atony Urecholine appears to be the drug of choice

Functional Dyspepsia (Hypoactive Upper Gastrointestinal Segment) —This condition is perhaps the most common gastrointestinal condition apart from func tional constipation that the practitioner is called upon to treat It is manifested by postprandial epigastric fullness belching nausea and generalized abdominal disten tion frequently chronic constipation is present Barium studies are negative The diagnosis is a clinical one with no characteristic laboratory findings although some investigators believe that the physiologic basis of the symptoms in this condition is gastroduodenal hypofunction

The cholinergic drugs Prostigmin Urecholine and Mecholyl are of no use in the treatment of this condition despite the theoretical attraction Experience has revealed that unpleasant side effects appear without the disappearance of symptoms Alcoholic beverages are occasionally helpful in this condition whether

Presently available digestants are almost ideal in that isolated organ replacement therapy is available (e g, pancreatin)· a more concentrated product, however, would be desirable

SELECTED REFERENCES

Antispasmodics

Bachrach W H ... t Dis 3 743, 1958
Chapman ... , M A, and Jones, C M Barium ... Tincture of Belladonna, and Placebos ... Man, Gastroenterology 23 234 1953
Cummins ... Drugs in the Management of Gastro- ... 56, 1957
Kern, F ... Experimental and Preliminary Clinical Study ... Amine, Banthine, Upon the Human Colon, ...
Posey, E ... I, and Code, C F The Effect of Certain ... Motility, Gastroenterology 11: 344, 1948
Sleisenger ... P Comparative Potency of Newer Anti ... Drugs ... Man, as Determined by a Sigmoid Motility Technique, Gastroenterology 27 829, 1954

Antacids

Burnett, C H, Commons, R R, Albright, F, and Howard, J E Hypercalcemia Without ... ncy, New Eng ...
Grace, W ... 31, 1948
Jeghers, J ... Treatment of ...
Kirsner, J ... Gastric Antacid and Anti secre tc ... ffect Upon Gastric Secretion in M ...

Cathartics

Almy, T ... Factors in the Production of Constipation, ...
Almy, T ... ve System, ed 3, Philadelphia, 1953, Lea & Febiger, pp ...
Cornell Conferences on Therapy The Rational Use of Cathartic Agents, New York State J Med 47 387, 504, 1947
Dreiling, D A, Fischl, R A, and Fernandez, O The Therapeutic Usefulness of Dulcolax (Bisacodyl), a New Nonpurgative Laxative, Am. J Digest Dis 4 311, 1959
Ingelfinger, F J The Treatment of Chronic Constipation, Ann New York Acad Sc 58 503, 1954
Poppel, M H, and Bangappa, C K Bowel Preparation for Roentgenologic Procedures Using a New Evacuant, Bisacodyl, Am J Roentgenol 81 696, 1959

Antidiarrheal Agents

Adler, H F, Atkinson, A J, and Fry, A C Effect of Morphine and Dilaudid on the Ileum and of Morphine, Dilaudid and Atropine on the Colon of Man, Arch Int Med 69 974, 1942
Emery, E S, Jr The Use of Absorbents in Gastro intestinal Diseases, J A M A 108 202, 1937
Kern, Fred, Jr, Almy, T P, and Stolk, N J Effects of Certain Antispasmodic Drugs in the Intact Colon, With Special Reference to Banthine (β Diethylaminoethyl Xanthene 9 carboxylate Methobromide), Am J Med 11 67, 1951

Stimulants and Digestants

Kern, Fred, Jr, and Almy, T P The Effect of Acetylcholine and Methacholine Upon the Human Colon, J Clin Invest 31 555, 1952
Schwat, R S, and Chapman, W B Clinical Uses of Neostigmine, M Clin North America 31 1238, 1947
Stafford, C F, Kugel, A I, and Dederer, A The Use of Urecholine in the Treatment of Post operative Distention, Surg Gynec & Obst 89 570, 1949

postoperative distention Neostigmine is an anticholinesterase material which potentiates the effect of endogenous acetylcholine on the smooth muscle of the gut

BETHANECHOL (URECHOLINE) —The usual oral dose is 10 to 30 mg, 3 or 4 times daily The usual subcutaneous dose is 2 5 to 5 0 mg 3 or 4 times daily Urecholine should never be given intramuscularly or intravenously It is the oral drug of choice in postoperative abdominal distention and both the oral and paren teral drug of choice in postvagotomy gastric atony Urecholine acts directly on the smooth muscle cells of the gut

METHACHOLINE (MECHOLYL) —The usual subcutaneous dose for abdominal distention is 5 to 20 mg The drug is unsatisfactory for oral use because of variable destruction in the gastrointestinal tract It is used in abdominal distention only if Prostigmin is not effective and then with a great deal of care Mecholyl acts directly on the smooth muscle of the gut

UNTOWARD EFFECTS —All cholinergic drugs may precipitate myocardial ischemia and asthmatic attacks in susceptible patients and they therefore should not be used in patients with coronary artery disease, bronchial asthma, or chronic lung disease When used parenterally atropine should be available for immediate intravenous administration

Alcoholic Beverages —These may be taken in any form 15 to 30 minutes be fore the heavy meal of the day in moderate amounts (equivalent of 30 to 60 ml of whiskey)

Hydrochloric Acid, Pepsin —These have no pharmacologic effects apart from placebo actions

Pancreatic Extracts —The physiologic dose is 3 to 4 Gm with each meal Enteric coated forms should be used to avoid gastric digestion The large number of pills necessary is a nuisance and may be avoided by using Viokase, which assays 6 times as much proteolytic activity as triple strength pancreatin Consequently 1 Gm of Viokase may be used 3 times daily

Dehydrochloric Acid (Decholin) —This is a true hydrocholeretic agent It is theoretically useful following plastic repairs of the extrahepatic biliary passages over foreign body tubes and in the rare condition known as sclerosing choledochitis in order to prevent the accumulation of sludge The usual dose is 0 5 to 1 Gm 3 times daily

A Design for the Use of Stimulants and Digestants

The gastrointestinal stimulants should be employed to therapeutic effect unless deleterious side effects supervene With the preparations currently available, minor side effects are to be tolerated for the therapeutic good The contraindications for cholinergic therapy should be constantly borne in mind

Replacement therapy with digestants should be in physiologic amounts except where merely placebo effect can be expected in which case more convenient smaller doses should be employed

Rational Basis for New Stimulants and Digestants

Present day stimulants have the disadvantage of generalized cholinergic ac tivity, as opposed to differential organ activity Side effects are thus inevitable

2 Arsonic Acid Derivatives
  a Carbarsone
  b Bismuth glycolylarsanilate (Milibis)
  c Balarsen
  d Acetarsone
  e Thiocarbarsone
3 Halogenated Hydroxyquinolines
  a Chiniofon
  b Diiodohydroxyquin (Diodoquin)
  c Iodochlorhydroxyquin (Vioform)
4 4-Aminoquinolines
  Chloroquine
5 Antibiotics
  a Tetracyclines
  b Erythromycin
  c Bacitracin
  d Fumagillin
  e Carbomycin
  f Penicillin—streptomycin combinations
6 Entamide (dichloroacethydroxy methylanilide)

The treatment of amebiasis is complicated by (1) selective tissue localization of different drugs, (2) the two forms of parasitic existence trophozoites and cysts, and their different biologic strains, (3) the bacterial population of the intestinal tract, (4) the general condition, especially the state of nutrition, of the patient, (5) the tolerance of the patient to different drugs, (6) equivocal evaluation of many drugs, and (7) reinfection

Since none of the drugs available satisfies the requisites of an ideal remedy, a combination of drugs is required depending on the severity of illness

The treatment of intestinal amebiasis may be considered broadly under three headings—acute amebic dysentery, chronic amebiasis, and metastatic amebiasis

Acute Amebic Dysentery—1 The treatment of a fulminant case of amebic dysentery may commence with the most potent amebicide, emetine The narrow margin of safety between the therapeutic dose and the toxic dose of this drug necessitates caution in its use The dose generally recommended is 1 mg per kilogram of body weight per day and never more than 65 mg per day for adults, 20 mg per day for children above 8 years of age, and 10 mg per day for those under 8 years The total dose should not exceed 10 mg per kilogram of body weight per course, spread over a period of 10 days, though the drug should only be continued long enough for a clinical response which is usually evident after 5 injections With the 5 day program electrocardiographic control is hardly necessary We employ the intramuscular injection of emetine 65 mg daily for the first 5 days The injections are made in the upper outer quadrant of the gluteal region, deep in the muscles and the patient apprised that the pain is usually considerable

2 Simultaneously the patient is given another effective antiamebic preparation, such as carbarsone (containing about 30 per cent metallic arsenic), comparatively well tolerated except in arsenic sensitive individuals It is given orally in doses of 0 25 Gm, 3 to 4 times a day, and continued for 10 days

3 This is followed by a course of tetracycline given orally, 1 5 Gm on the first day and 1 Gm daily thereafter in divided doses for a week to 10 days or

Chapter 23

THE CHOICE OF DRUGS FOR INTESTINAL PARASITISM

B H Kean, M D, and

A B Choudhury, M B, D Phil

INTRODUCTION

The choice of drugs in the treatment of parasitic diseases requires knowledge of the triumvirate formed by the parasite the host and the drugs as well as their interrelationships Successful chemotherapy depends on a precise identification of the offending parasite, on an estimation of the intensity of infection and extent of injury to the host on the accessibility of the site of damage on a cautious assessment of the patient s general condition and on an appropriate selection of drug weighing parasiticidal efficacy against adverse effects

Unlike antibacterial efforts radically revolutionized by the advent of antibiotics the evolution of antiparasitic measures has been slow and gradual some of the obstinate parasitic diseases continue to defy all therapeutic measures The relatively unsatisfactory progress of this branch of chemotherapy has been due to its dependence on the empirical approach and inadequate knowledge of parasitic physiology In recent years however information on parasitic metabolism and on host parasite relationship has reduced the indiscriminate screening of compounds and hastened the pursuit of more effective drugs Since the publication of the first edition of this text several important additions have been made to the parasitologist s pharmacopeia

CLINICAL CONSIDERATIONS

Amebiasis—Amebiasis caused by *Endamoeba histolytica* is perhaps the most important parasitic malady afflicting mankind now that malaria can be successfully controlled Although many antiamebic agents are available, unfortunately none of them deserves to be listed as the drug of choice The drugs currently recommended belong to the following groups

1 Alkaloids of *Cephaelis ipecacuanha*
Emetine hydrochloride and emetine bismuth iodide

mended because of the serious nature of the disease Emetine, 65 mg, is istered daily to an average adult by the intramuscular route for 10 days, a currently chloroquine is given orally, 1 Gm daily for the first 2 days, and (daily for the next 18 days It should be emphasized that hospitalization, b frequent electrocardiograms, and close observation are necessary when is used in this manner Widening of the QRS complex and prolongation P R interval warrant discontinuation of emetine Repetition of the course drug holiday of 2 weeks is sometimes desirable, but emetine should be gi only 6 or 7 days Therapeutic response to these drugs, however, appear early and is often of diagnostic value All patients with metastatic amebic tions should also receive a course of treatment for intestinal amebiasis beca emetine chloroquine combination does not deal efficiently with an intesti fection

Surgical intervention in metastatic amebiasis should not be undertak cept as a last resort

So called diffuse amebic hepatitis, characterized by hepatomegaly, l tenderness fever, leukocytosis, and laboratory evidence of hepatic dysfunct a patient with intestinal amebiasis, is probably nonspecific in nature and ass with ulceration of the intestinal tract, amebic or otherwise, it disappears un fully following elimination of the intestinal cause

Giardiasis —Of the intestinal flagellates of man, Giardia lamblia is mo quently considered pathogenic, although there is still dispute over its precis The morbid changes in the small intestine ascribed to the heavy colonization *lamblia*, the frequent association of either a diarrheic syndrome or of one sii ing biliary disease, and their ready response to treatment, provide ample jus tion for specific therapeutic measures

For the last two decades, quinacrine (Atabrine) has been the drug of c *It is given orally 0 1 Gm, 3 times daily for 1 week, this course being repeated* a fortnight Reappearance of the parasites is noted in 10 to 30 per cent patients necessitating a third course

Chloroquine, being less toxic especially in children has been used i treatment of giardiasis But the rate of success is not high nor are results consi Other drugs such as Acranil and diiodohydroxyquin and intravenous injectic Urotropin cannot be recommended In children the doses of quinacrine chloroquine should be reduced but since neither drug is very toxic, the sche may be higher than weight formulas would indicate

Trichomoniasis —*Trichomonas hominis* is a much commoner parasite in intestine of man than is generally recognized It is frequently associated with intestinal disorders and hence its role as the sole cause of diarrhea is often tioned Carbarsone, 0 25 Gm, 3 times daily for 10 days, has proved effec although recurrences are not rare Tetracycline, 1 Gm daily in divided dose 1 week, is an alternative

Balantidiasis —*Balantidium coli* is the only bona fide ciliate to parasitize r Records of human infections are not numerous The parasite is able to invade the cosa of the large intestine and reach the submucosa where it causes rapid destruc

unless there are troublesome gastrointestinal disorders such as nausea, vomiting and diarrhea

4 The schedule is completed with a course of diiodohydroxyquin (containing about 65 per cent iodine), another satisfactory antiamebic drug contraindicated only in persons with gross liver damage and in those with iodine idiosyncrasy It is used in doses of 0 65 Gm taken orally 3 times a day before meals for a period of 20 days

5 To this may be added a course of chloroquine It is administered orally, 1 Gm daily for the first 2 days, and 0 5 Gm a day subsequently for 15 days This last drug is considered a safeguard against any possible metastatic or extraintestinal amebic lesion which may have escaped clinical recognition

A cure rate of over 90 per cent can be anticipated with this regimen

Evaluation of the success of therapy is difficult because the elimination of parasites and not the amelioration of clinical symptoms constitutes the criterion of cure The problem is complicated by the so called "negative phase" during or shortly after specific therapy when absence of parasites in the stool does not signify cure To have significance, examination of stool should, therefore, be done 1, 3 6, and 12 months following completion of treatment To avoid fallacies likely to be attendant on a single examination each re-evaluation should include three stool examinations, with at least one following the use of a saline cathartic, and should be supplemented by a proctoscopic examination If "follow up" study reveals the presence of parasites, the whole course should be repeated

Chronic Amebiasis —By chronic asymptomatic," or nondysenteric amebiasis is meant the stage of disease in which cysts or trophozoites of *E histolytica* are found in a routine examination of the stool of an asymptomatic" patient While some of these patients may be in apparent good health without specific complaints, the majority have vague intestinal discomfort or other evidences of disease of a protean nature The potential for an acute flare up and concern for the public welfare leave little justification for complacency in the treatment of these carriers There is, therefore every reason to recommend treatment although emetine injections should be omitted from the regimen proposed for patients with acute amebic dysentery A successful program is carbarsone, 250 mg, 3 or 4 times daily for 10 days followed by Diodoquin 0 6 Gm 4 times daily for 14 days

Our British colleagues prefer emetine bismuth iodide (E B I) This reddish powder is insoluble in water and is better administered in gelatin capsules than in enteric coated tablets which often pass through the intestinal tract unaltered The proper dose is 65 mg 3 times daily for 10 to 12 days Children may be given 1 to 2 mg per kilogram of body weight If vomiting occurs, the drug may be stopped for a day or prochlorperazine dimaleate like compounds (Compazine) may be used The symptoms of toxicity which occur when emetine hydrochloride is used by intramuscular injection are very rare when emetine bismuth iodide is used orally

Metastatic Amebiasis —In the treatment of metastatic amebiasis, particularly amebic abscess of the liver, emetine has long been recognized as specific, but recently chloroquine has been found to be almost as effective The best results are obtained when both drugs are used and such a combination is recom-

compounds is best A number of piperazine salts, the citrate, phosphate, diphenyl acetate, etc, have been introduced by different pharmaceutical houses but they are basically similar In the dosages recommended, piperazine produces few side effects although an occasional patient may experience nausea, vomiting, urticaria, general muscle weakness, or blurred vision These symptoms disappear rapidly when the drug is discontinued

An effective dosage schedule of piperazine citrate is 1 Gm daily for children up to 30 pounds in weight, 2 Gm for those weighing 30 to 50 pounds 3 Gm for those weighing 50 to 100 pounds, and 3 5 to 4 Gm for those over 100 pounds The dose in wafer or syrup form is given once daily for 2 consecutive days, and the program may be repeated after 1 week No accessory purgation is required

The simplicity, safety, and efficiency of the piperazines are eliminating the use of many compounds which were favored in the past Santonin and oil of chenopodium are no longer considered useful Diethylcarbamazine (Hetrazan), a substituted piperazine derivative, is not as effective as piperazine

Hexylresorcinol, however, has good ascaricidal value but is somewhat toxic It is administered on an empty stomach in the morning, the dose being 1 Gm for adults 0 8 Gm for children between 6 and 10 years of age, and 0 6 Gm for those under 6 years The capsules must be swallowed without being cracked open or chewed to avoid irritation of the buccal mucosa A saline purge may be administered 2 hours later to facilitate removal of dead or dying worms Food is proscribed for 4 to 5 hours to prevent gastric colic and to insure greater efficacy of the drug

Two n ... iazinine iodide (Delvex), and bephenium ... e decided ascaricidal properties but proper (... not available The usefulness of pyrvinium pamoate (Povan) is also being studied

Enterobiasis —*Enterobius vermicularis*, popularly known as pinworm or thread worm, is most common in temperate climates Though essentially a short lived parasite, which takes 15 to 28 days to complete its life cycle and seldom survives more than 8 weeks, the ease of reinfection accounts for the protracted course of the disease and the difficulty of effecting a cure The negligible injury that this parasite inflicts is often exaggerated by the psychologic implication of 'having worms Successful treatment requires rigid enforcement of hygienic measures and simultaneous treatment of other members of the household who commonly serve as a reservoir for reinfection

The unsubstituted piperazine salts are highly recommended for the treatment of enterobiasis Piperazine, available in wafer or syrup form, is given once daily for 7 consecutive days according to the following schedule for children up to 15 pounds in weight, 250 mg , 15 to 30 pounds 500 mg , 30 to 60 pounds, 1 Gm , and for those over 60 pounds, 2 Gm The course may be repeated after 1 week or given at regular intervals, e g every 3 months to keep the worm burden low in those who are reinfected A cure rate of approximately 80 per cent may be expected with piperazine although greater efficiency has been recorded by some

A new compound, pyrvinium, may replace piperazine as the drug of choice in the treatment of enterobiasis Pyrvinium pamoate sold under the trade name

The best results reported thus far in the treatment of this infection have been with oxytetracycline (Terramycin), 1 5 to 2 Gm daily in divided doses, given for a period of 10 days Carbarsone, 250 mg taken 4 times a day for 10 days, is also effective

Hookworm Infection—Hookworm infection (*Necator americanus* and *Ancylostoma duodenale*) is one of the most prevalent helminthic diseases of man, particularly in warm climates The worms stealthily sap the vitality of the patient long before symptoms suggest the diagnosis If unattended the infection exacts a devastating economic and medical toll in areas where it is endemic

Although some patients may require preliminary supportive and antianemic measures, in most the anthelmintic drugs may be used at the outset

(1) Tetrachloroethylene remains the drug of choice It is almost devoid of any toxicity provided its nonabsorption is ensured by the absence of alcohol and absorbable fat in the intestinal lumen To guarantee its therapeutic potency, the drug should be fresh following storage in a cool, dark place The standard procedure is to administer the drug early in the morning to a patient with a fasting stomach, following fat free liquid diet the night before The single dose is 4 ml for an adult and 0 25 ml per year of apparent, not chronologic, age in the case of children For the adult a saline purgative sodium sulfate (Glauber's salt) 30 Gm, is given 3 hours later in a glass of water Recent reports suggest that better results may be obtained if the saline cathartic is omitted Food is withheld for 4 to 6 hours following treatment

Success of treatment should be determined upon the re examination of stool a week later, the course may be repeated if necessary A worm removal value of approximately 90 per cent has been reported with a full therapeutic dose of tetrachloroethylene

This drug is however unsuitable when hookworm infection and ascariasis coexist because tetrachloroethylene stimulates *Ascaris lumbricoides* to activity and grave abdominal emergencies such as intestinal obstruction or even perforation may follow migration of the parasite To avoid this situation the treatment for hookworm infection should be preceded by one for ascariasis

A new series of anthelmintics the salts of bephenium including bephenium hydroxynaphthoate (Alcopara) bephenium iodide and bephenium embonate have been studied for the treatment of dog hookworm *Ancylostoma caninum* and human hookworm, especially *Necator americanus* Although dose schedules toxicity and efficiency of these compounds have not been evaluated fully the [illegible]

[illegible]

3 G [illegible]

pro[illegible]

thought to be too dangerous—and also in those also infected with *Ascaris lumbricoides*

Ascariasis—*Ascaris lumbricoides* the large intestinal roundworm is one of the most dangerous of human parasites For its eradication one of the piperazine

blue and only slightly soluble in water, it is ordinarily not absorbed
intestinal tract, and stools are stained blue

Although careful clinical studies have revealed no hematopoietic,
hepatic damage following the administration of therapeutic doses, acce
the drug by patients has been poor in our experience Intense nausea,
and some abdominal cramps with diarrhea are often reported on the fi
treatment and make continuation of the regimen difficult These limit
not important in enterobiasis and ascariasis since other drugs are ava
these infections In strongyloidiasis, which may be a serious infection
trichuriasis, in which no other drug is adequately effective, means should
to persuade the patient to complete the treatment.

Two methods have proved effective (1) halve the recommended
treat for twice as long and (2) use antiemetics and tranquilizers such as
perazine dimaleate (Compazine) the day before treatment is started and
first 4 days

The following is the recommended total daily dose which is divided i
doses and given for 10 to 14 days unless it is decided to halve the dose an
ister for 20 to 28 days children 20 to 30 pounds, 200 mg , 30 to 40 pou
mg 40 to 50 pounds 400 mg , 50 to 60 pounds, 500 mg , and for ad
children over 60 pounds, 600 mg

Another drug somewhat effective in this condition is gentian violet m
administered orally in the form of enteric coated tablets The adult dose is
3 times a day, given with meals for a period of 16 days The dose for
is 10 mg daily for each year of apparent age Nausea, vomiting and coli
in the abdomen at times do not permit completion of the course Patients
a poor response with standard oral therapy may be treated with 25 ml of
cent solution of the drug by transduodenal intubation

Diethylcarbamazine (Hetrazan) has been reported to be useful in strongy
when administered orally in doses of 2 mg per kilogram of body weight
daily for 20 days but this drug has not been successful in our experience

Trichuriasis—Only heavy infections with *Trichuris trichiura* or wh
have been associated with symptoms of diarrhea, mild infections may be r
as innocuous not requiring energetic treatment

Until recently no drug could be recommended even with mild enth
Dithiazanine iodide (Delvex), however, is very effective and if its toxic ma
tions especially those which occur on the first or second days of its use
kept to a minimum a very high rate of cure possibly 85 to 90 per cent,
expected The dose schedule is identical with that described for the treatm
strongyloidiasis but should be maintained only for 5 days The concurre
of Compazine and other preparations is advisable in many patients (see dis
of dithiazanine under Strongyloidiasis)

In heavy infections a high retention enema with hexylresorcinol may b
After a preliminary enema to clear the large intestine of fecal accumulatio
perianal area and the buttocks are covered with a coating of petrolatum to p
... hexylresorcinol This is followed by the retention

of Povan (formerly Poquil and Vanquin) is the pamoate salt of a complex cyanine dye [6 dimethylamino-2 [2 (2 5 dimethyl 1 phenyl 3 pyrryl)vinyl] 1 methylquinolinium chloride] It is available as a coated tablet containing 100 mg of the pyrvinium base and also as a red pleasant tasting fruity suspension containing 10 mg of base per milliliter

The drug is not absorbed from the intestinal tract toxic symptoms including nausea vomiting and diarrhea are extremely rare Patients should be warned that pyrvinium colors the stools bright red and that the suspension if spilled, will stain clothing and other materials

Although several regimens have been tried and proved effective pyrvinium is

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of body weight may be given and since overdosage is not dangerous one may safely add a dose unit for any proportion of 20 or 40 pounds For example a 50 pound child may be given 3 teaspoonfuls (15 ml) of the suspension and a 140 pound adult may be given four 100 mg tablets

Whether piperazine or pyrvinium is used simultaneous treatment of all members of the household is recommended If the patient is exposed to recurrence at school period c treatment e g every 2 or 3 months may be necessary

The following adjuvant measures are advised (1) A daily shower *in the morning* to remove the eggs deposited in the perianal region during the night (2) Regular application of an antipruritic ointment over the perianal area at bedtime Mercury ointment (in petrolatum) or Perazil (chlorcyclizine 1 per cent) cream serves the purpose well (3 The use of close fitting shorts under one piece pajamas locked by safety pins or ties at night (4) The regular trimming of the child s nails and the scrubbing of his fingers with a brush after each visit to the toilet and the daily use of disinfectants on the toilet seats

Gentian violet medicinal (methylrosaniline) antibiotics tetrachloroethylene phenothiazine egressin gamma benzene hexachloride high enemas infusions of of quassia chips and antihistaminics are not recommended

A patient is generally considered cured when 7 consecutive perianal transparent cellophane swabs show no oxyurid ova a swab is taken each morning before bowel movement or bath commencing one week after the end of treatment In clinical practice two or three negative swabs are adequate

Strongyloidiasis —*Strongyloides stercoralis* though commonly encountered in warm climates has not infrequently been recorded in temperate and even in cold regions The usual intestinal symptoms are abdominal discomfort dyspepsia and diarrhea alternating with constipation tender liver and eosinophilia

that of any other drug Since dithiazanine is also used for the treatment of trichuriasis and since its broad spectrum anthelmintic activity extends to pinworm and roundworm, it may be considered in some detail

Dithiazanine is a polymethine dye 3 3 diethylthiadicarbocyanine iodide Being

ning a saline purgative (30 Gm of sodium sulfate) is given Early next morning on the empty stomach, a sedative such as phenobarbital, 60 mg, is administered orally and a duodenal tube is inserted An hour later, 1 Gm of the quinacrine suspended in 20 ml of water is introduced through the duodenal tube and washed down with a small amount of water to prevent loss of drug in the syringe and in the tube In case the oral administration is decided upon, 2 tablets (0 2 Gm) are given at 10 minute intervals for a total of 10 tablets (1 Gm), a little sodium bicarbonate is added each time to counteract the emetic tendency likely to attend oral medication Two hours after the drug is administered, a saline purgative (sodium sulfate 30 Gm) is given If a satisfactory purgation is not achieved, a soapsuds enema should be given, after which normal diet is permitted

For 48 to 72 hours following this therapy all stool specimens should be examined carefully for the scolex or head of the worm The finding of the scolex indicates total expulsion of one worm but the possibility remains that more than one worm was harbored by the patient Inability to find the scolex does not necessarily mean failure of treatment since the scolex may have been digested, lodged *in the large intestine, or lost in the large bulk of worm expelled Hence the final* criterion of cure is the absence of eggs and segments in the stool for a period of 6 months following treatment The rate of success with this technique is more than 90 per cent

Another drug effective against tapeworm infections is oleoresin of aspidium It may be administered through the duodenal tube as a mixture of 6 Gm of the freshly prepared oleoresin of aspidium, 30 ml of acacia, and 30 ml of a concentrated solution of sodium sulfate, no posttreatment purgative is required

The drug may also be administered orally, 1 2 ml every 30 minutes for 3 doses (total 3 6 ml) This is followed in 2 hours by a saline purge But a greater degree of toxicity and the difficulty in obtaining a fresh drug militate against the use of this preparation

Recently a modification of the method prepared by De Rivas in 1932 has been designed by Rosen and Kiefer

> Before the treatment is begun the following articles should be ready at the bedside (1) a Rehfuss tube, (2) a 50 ml syringe, (3) a bottle of glycerin, (4) a bottle of saturated magnesium sulfate solution (5) a thermometer (preferably centigrade), and (6) 500 ml of sterile saline solution
>
> The procedure for treatment is as follows (1) Pass a Rehfuss tube into the stomach (2) Turn the patient on his right side and allow the tube to pass into the duodenum (3) Check the tube by fluoroscope to be certain that the tip is well down in the second or third portion of the duodenum, beyond the ampulla of Vater (4) When certain the tube is in position, introduce 1½ oz of magnesium sulfate solution through the tube (5) Then introduce immediately 1½ oz of glycerin (6) Then introduce immediately 2 oz of a mixture of equal parts of magnesium sulfate and glycerin (7) Then introduce immediately 500 ml of the sterile saline solution which has been warmed to a temperature of 54 to 60° C or 130 to 140° F A bucket and a bedpan should be ready in the patient's room The bucket should contain warm water or saline solution so that if the worm is obtained it can be preserved and identified

Of the 40 patients treated by this method 36 were considered cured, in 31 the scolex was recovered and in 5 no evidence of infection was found in 1 to 5 years

temperature, to which about 30 Gm of fine kaolin may be added to m colonic cramps This may be repeated one week later

Trichinosis—Although infection with *Trichinella spiralis* generally is causing only a "digestive upset" followed by muscular pain, it may be respor for serious and occasionally fatal disease The diagnosis of trichinosis, unfc nately, is difficult to establish before larvae have reached the muscles in g numbers

With timely suspicion of the disease during its early intestinal phase atter may be made to dislodge the adult worms before they are sheltered deeply in intestinal mucosa and before larvae are produced Repeated administration sodium sulfate may eliminate some of the adults so that the number of larvae ava able for systemic invasion is minimal Encouraging response has been reporte recently with the use of piperazine citrate in a dosage of 2 to 3 Gm. daily for week, removing many of the adults from the intestinal tract Since the drug not toxic, its use is urged, although our own results have been disappointing

Specific therapeutic agents employed against trichinosis during the stage of systemic invasion have failed To alleviate the patient's distress, palliative meas ures such as bed rest, analgesics, sedatives, adequate fluids, balanced diet, saline cathartics, etc are the essentials of treatment Steroids such as ACTH, cortisone, and similar preparations are believed to suppress the cellular inflammatory reac tion in affected muscles and to depress the eosinophilia They are extremely useful for symptomatic relief and may be valuable in severe infections Although the statistical evidence currently available does not provide support for the view that steroids alter the course of the disease, the drugs do afford the clinician the oppor tunity to offer his patient considerable relief—especially in serious situations

Tapeworm Infection—Of the cestodes or tapeworms inhabiting the intestinal tract of man four deserve consideration *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenol epis nana* (dwarf tapeworm) They have been held responsible for varying grades of vague gastrointestinal and nervous disturbances and for systemic disorders of bizarre nature attributed to the mechanical irritation, toxic" products of the worms, and their ability to deprive the host of the nutritional requirements The larvae of *T solium*, however, are certainly dangerous since the parasite may lodge in any organ of the body, forming the stage known as *Cysticercus cellulosae*

For the treatment of these worms, quinacrine (Atabrine) is considered best because of its high degree of efficacy and relatively low toxicity Being a gastric irritant, the drug may cause nausea and vomiting when administered orally Direct instillation by means of transduodenal intubation ensures a greater concentration of the drug at the required site and obviates the risk of vomiting It should be emphasized that in *T solium* infections reverse peristaltic waves, resulting from gastric irritation may facilitate the transport of the eggs high in the duodenum, thus adding to the danger of cysticercosis which, unfortunately, is not amenable to any drug therapy hence intubation should always be used in this infection

The success of treatment depends a great deal on the careful attention to the preparation of the patient The day before treatment the patient has a light l... nd a liquid dinner, and only sips of water are allowed after ...

2 Gm may be given in divided doses for 3 to 5 days Nausea vomiting insom and reddish brown discoloration of the palms and soles may necessitate reduct in the dose

Other Trematode Infections —Intestinal trematodiasis occasionally results fr infection with intestinal flukes, viz, *Fasciolopsis buski* (fasciolopsiasis), *Heteroph heterophyes* (heterophyasis), *Metagonimus yokogawai* (metagonimiasis), *Gastro coides hominis* (gastrodiscoidiasis), *Watsonius watsoni* (watsoniasis), and the li flukes, viz, *Fasciola hepatica* (fascioliasis), *Clonorchis sinensis* (clonorchiasis), *Opisthorchis felineus* (opisthorchiasis)

Varying grades of gastrointestinal disturbances with or without other syster disorders are produced by these parasites, and therapeutic efforts are justified ev if they are inefficient

For the treatment of infection by intestinal flukes the drugs found useful tetrachloroethylene and hexylresorcinol Emetine is considered effective in t treatment of the liver fluke infection, fascioliasis and is employed in the sa manner as for the treatment of amebiasis Success has been reported in the tre ment of the liver fluke infections clonorchiasis and opisthorchiasis with genti violet medicinal 60 mg orally, 3 times daily with meals for 30 days Anoth drug reputedly effective for this purpose is chloroquine administered orally, (Gm daily for 4 weeks Our own experience with antitrematode measures has be depressing

RATIONAL BASIS FOR DRUG THERAPY OF INTESTINAL PARASITIS

The rapid introduction of therapeutic agents for the treatment of intestin parasitism, the multiplicity of preparations which are pharmacologically simil but have been altered somewhat to permit proprietary labeling, and the differe evaluations placed on the efficacy of important drugs by experts in the field ha caused considerable confusion to the clinician

For example, in the treatment of intestinal amebiasis there are those who insi on the use of emetine whereas others consider the drug unnecessary or dangerou the halogenated quinolines such as diiodohydroxyquin are thought to be ve effective by some and almost useless by others In annual succession, bacitraci Aureomycin Terramycin, and fumagillin were described as the drug of choice unt the percentages of reported cures dropped rapidly

The merits of an ideal drug for the treatment of intestinal parasitism can b conveniently listed as follows (1) maximum efficacy, (2) minimum toxicity, (3 good margin of safety between the therapeutic and the toxic doses (4) broa spectrum of activity (5) suitability for children and the critically ill (6) ease c administration in an agreeable form, (7) short duration of treatment, (8) lo cost, and (9) easy availability

One may anticipate the appearance within the next few years of many dif ferent drugs, some with entirely new pharmacologic principles, for the eliminatio of parasites e g, folic acid antagonists such as Daraprim for the prevention o malaria Cautious evaluation of claims must be made and enthusiasm withhel until several reports from reliable investigators in various parts of the world ar

Chapter **24**

THE CHOICE OF DRUGS FOR DISEASES OF THE HEART

Walter Modell, M.D.

THE CHOICE OF A DIGITALIS MATERIAL

INTRODUCTION

The problem of the choice of a digitalis material is as old as its use in medicine. In 1785, Withering debated whether foxglove or squill was the better for dropsy. He chose the former because of greater consistency in effectiveness, with less nausea and vomiting. While there is universal agreement that Withering's contribution to medicine was a great one, there is no such agreement that he made the proper choice of a digitalis material. Doubt along these lines has increased with the introduction of still more digitalis materials.

If anything Nature has been overgenerous with digitalis materials; they are to be found in the skin of toads and in weeds in back yards; they are found in plants indigenous to all corners of the earth. It is certainly something for which to be grateful that chemists have not yet learned how to synthesize members of this group of drugs to further complicate the problem of their choice. The use of digitalis has geographic features. The American market has a large armamentarium of its own; foreign usage differs depending often on the availability of natural sources of digitalis materials.

CLINICAL APPLICATIONS

The differences between the digitalis materials are quantitative; qualitatively they are all similar; the basis of a choice lies in the way the differences in parameters of action make one or another better suited for a specific clinical need. The discussion of the actions of digitalis which follows may be applied to all members of this large group.

Heart Failure.—There is a clinical impression that digitalis is not equally effective in all cases of heart failure. However, it can be stated categorically that unless there is a specific contraindication, e.g., digitalis intoxication or ventricular tachycardia, digitalis is invariably indicated in heart failure.

SELECTED REFERENCES

Anderson, H H, Bastick, W L, and Johnstone, H C Amebiasis, Pathology, Diagnosis and Chemotherapy, Springfield, Ill, 1953, Charles C Thomas

Belding, D L Basic Clinical Parasitology, New York, 1958, Appleton Century Crofts, Inc

Brown, H K, Chan, K F, and Hussey, K L Treatment of Enterobiasis and Ascariasis [illegible]

[illegible] Davis & Co

Forkner, C. E Amebiasis, Practitioners Conference Volume 5, New York, 1957, Appleton-Century Crofts, Inc

Forkner, C [illegible] Infection [illegible] Practitioners' Conference Vol [illegible]

Frye, W [illegible] son, C B, Jr An E[illegible] Trop Med & Hyg 6[illegible]

Goodwin, L G, Jayewardene, L G, and Standen, O D Clinical Trials With Bephenium Hydroxynaphthoate Against Hookworm in Ceylon, Brit M J 1. 1572, 1958

Kean, B H The Treatment of the Commoner Parasitic Diseases, M Clin North America 37 903, 1953

Manson Bahr, P Amoebiasis and Amoebic Dysentery, Brit J Clin Pract. 11 709, 1957

Monto, A S The Liver in Ulcerative Disease of the Intestinal Tract Functional and Anatomic Changes, Ann Int Med 50 1385, 1959

Rodrique [illegible]

Rogers, L [illegible]

Rosen S [illegible]

Sodeman, [illegible] J A M A 148 285, 1952

Swartzwelder J C, Frye, W W, Muhleisen, J P, Miller, J H, Lampert, R, Chararria, A P, Abadie S H, Anthony, S O, and Sappenfield, R W Dithiazanine, an Effective Broad Spectrum Anthelmintic, J A M A 165. 2063, 1957

Tropical Diseases Bulletin, Bureau of Hygiene and Tropical Diseases, London (This publication provides a "running' summary of all new advances in the field)

HEART FAILURE AND AURICULAR FIBRILLATION —The combination of heart fa ure with auricular fibrillation provides the cardiodynamic setting for which digita *seems to be best suited* Digitalis is so much more dependable in this situation th *in other forms of heart failure* that it strongly suggests that here, in addition increasing the force of ventricular contraction, the direct action of digitalis to sl ventricular rate adds to its usefulness However, the superior results may be d to the fact that digitalis can be used with greater ease and safety than in oth types of heart failure, and a satisfactory degree of digitalization, therefore, is mo consistently obtained, for the consistent slowing of the ventricular rate by digita provides an end point of drug action found in no other clinical condition, th ventricular rate can be used as a sensitive guide to dosage

The choice of a digitalis preparation depends largely on urgency If rap action is needed, a parenteral preparation should be chosen, if there is time, dig toxin is the drug of choice

HEART FAILURE WITH RAPID NORMAL SINUS RHYTHM —The action of digital to slow the heart rate is indirect in this situation and depends entirely on whethe the digitalis improves myocardial function sufficiently to bring about reflex slow ing In so far as digitalis is indicated in all cases of heart failure, it is indicate here, the particular material depends on the urgency

AURICULAR TACHYCARDIA —As explained elsewhere (page 409), digitalis useful in the relief of auricular tachycardia In this situation, maneuvers whic intensify vagal tone (eyeball pressure, carotid sinus pressure, emesis) may slow th tachycardia temporarily or bring it to an end When these fail, digitalis may b used to increase the sensitivity of the sinus node to the vagal tone *After the effect* of digitalis have developed, the maneuvers once ineffective, may terminate a sinu tachycardia The situation calls for a rapid acting digitalis material The par enteral route is probably also preferable

AURICULAR FLUTTER —The uses and choice of a digitalis material in auricula flutter are considered in detail on page 409

AURICULAR FIBRILLATION —The uses and the choice of a *digitalis material* i auricular fibrillation are considered on page 409

HEART BLOCK —The uses and the choice of a digitalis material in heart block are considered on page 411

OTHER CARDIAC ARRHYTHMIAS —Digitalis exerts no pharmacologic action which can be counted upon per se to restore a normal sinus rhythm in the case of cardiac arrhythmia *arising from an ectopic focus* *Its special action* in auricular flutter is described elsewhere (page 409) and involves the induction of auricular fibrillation, while its action in auricular fibrillation is to preserve the arrhythmia *while slowing the ventricular rate* *It is probably* dangerous in ventricular tachy cardia and fibrillation

There are instances, however, in which, following the administration of digi talis, arrhythmias disappear and normal rhythm returns In such instances it must be assumed that the arrhythmia was secondary to the relative hypoxia or cardiac distention of the heart failure and that, with the relief of the heart failure, the cause of the arrhythmia was removed This result of digitalization is not regu larly seen and cannot be counted upon On the other hand, since digitalis is indi

LEFT HEART FAILURE.—Left heart failure is characterized by increased fluid in the pulmonary bed. At times it is seen as frank edema, with râles, acute pulmonary edema, paroxysmal nocturnal dyspnea, etc. At other times, râles cannot be heard nor can fluid be demonstrated by clinical examination. In the latter, the only evidence for excess fluid in the pulmonary bed is the presence of dyspnea on effort and orthopnea. These symptoms are accepted by some, but not all, as the earlier manifestations of left heart failure caused by the transudation of fluid into the intercellular spaces, small in amount, but sufficient to interfere with respiratory function. Subsequent development of frank pulmonary edema in these patients tends to substantiate the concept. It is also conceivable that even without transudation of fluid, but merely on the basis of poor circulation through the pulmonary bed, symptoms of defective respiratory exchange may develop.

Although the left heart failure syndrome is the result of deficiency in cardiac action and although digitalis is indicated, the effects of digitalis alone are not impressive and do not satisfy the clinical needs of most patients.

The basis of this form of cardiac failure may be speculated upon, for it may explain why digitalis cannot help much. Left heart failure is commonly seen as a consequence of hypertension and rheumatic heart disease with a tight mitral valve. The difficulty in these situations, in the early stages at least, is not so much that the cardiac muscle is feeble as that a normal or nearly normal myocardium cannot cope with the mechanical barrier to the flow of blood: the tight mitral valve in one case and the constricted arteriolar bed in the other. Further increase in the force of contraction by digitalis cannot be expected to diminish appreciably the transudation of fluid due to the attempt to force fluid at a high pressure through a constricted passage.

In the acute attack of left heart failure, e.g., that seen after an acute myocardial infarction, digitalis may perhaps be expected to accomplish more. Here the need is urgent. In this instance, a rapid acting preparation administered parenterally is usually required.

RIGHT HEART FAILURE.—While our understanding of the mechanism of right-heart failure is more confused than that of left heart failure, there is greater agreement that the digitalis materials are useful. Peripheral edema in the extremities and even the abdomen may disappear after a diuresis induced by the effects of digitalis.

Since right sided heart failure per se, even with massive edema, does not threaten life, urgent measures are not usually necessary. Edema of the extremities can be removed more gradually because, unlike edema in the pulmonary bed, it does not impinge on vital function. Where accumulation of ascitic fluid causes distress, the quickest and surest method of relief is paracentesis.

In my hands, the results with digitoxin have been satisfactory in right sided heart failure for digitalization as well as maintenance. With few exceptions, I find it the drug of choice for digitalization and maintenance. The relatively low cost of the preparation is another consideration. On the other hand, when a parenteral preparation is necessary to obtain results quickly, other digitalis materials are more desirable.

due to a shift from supraventricular to idioventricular pacemaker In other situations, prolongation of the conduction time, partial block, or complete auriculoventricular dissociation is undesirable

MYOCARDIAL AUTOMATICITY —Digitalis increases myocardial automaticity, inducing premature ventricular contractions, coupling, ventricular tachycardia and ventricular fibrillation as well as auricular disturbances These are toxic actions This action of digitalis may, however, be used to increase the idioventricular rate in heart block

VOMITING —Vomiting is a toxic effect which results from both local and systemic actions of digitalis These are discussed below

OTHER CENTRAL NERVOUS SYSTEM EFFECTS —In the rat, convulsions are seen consistently after squill, but also after other preparations Convulsions are not seen in man but central stimulation has been reported The action of digitalis on vision is a central nervous system effect This sign is a substantial warning that further digitalization may be dangerous

DIURETIC ACTION —From time to time, the question of a direct action of digitalis on the kidneys to cause diuresis is brought up There is old evidence that this does occur in animals It is more often observed when a very rapid acting digitalis material such as acetyl strophanthidin is used The action is inconsistent and always brief Therefore, while there is evidence of a diuretic effect of digitalis exerted through a direct action on the kidney, there is no evidence that this is a clinically significant digitalis action As a matter of fact, it is probably of no practical importance at all

Parameters of Action —Digitalis materials all share the actions just described their major differences lie in the parameters of these actions, and it is on the basis of these differences that one or another is the more desirable in a particular situation

POTENCY —Digitalis materials vary greatly in potency Ouabain the most potent of pure glycosides in common use has a cat unit value of 0 1 mg Digitoxin, which is one of the less potent of the commonly used purified glycosides has a cat unit value of 0 4 mg The partially purified materials and the crude mixtures are far less potent Thus an average specimen of the leaf of *Digitalis purpurea* has about one thousandth the potency of digitoxin

The significance of these differences in potency is less impressive than their magnitude seems to suggest Provided the appropriate dose is administered and absorption is taken into account, the same therapeutic effects can be produced despite the differences in absolute potency This is why the concept of the human unit of digitalis, which involves absorption in the human gastrointestinal tract, is so useful, it reduces all the digitalis glycosides to a common biologic denominator

TOXICITY —This may be separately considered as local action in the gastrointestinal tract due to the physical and chemical nature of the drug and as systemic actions representing the effects of the drugs after they have entered the circulation Hypersensitivity to digitalis materials occurs so rarely that no statement can be made about their relative potential or danger in this regard

Local Irritant Action Local irritant actions in the gastrointestinal tract are usually considered to be minor toxic symptoms and not a threat to the patient

cated in virtually all cases of cardiac failure, this indirect effect is likely to be obtained in every instance in which the full benefits of digitalis are obtained through its proper use in the treatment of heart failure

CARDIAC PAIN —Digitalis does not relieve cardiac pain When it appears to do so, it may be presumed (as in the case of the arrhythmias) to be secondary to the relief of heart failure

WEAKNESS AND FATIGUE —Digitalis has no direct effect on weakness and fatigue in heart disease Where its use is followed by improvement in these symptoms it must be assumed that the symptoms were manifestations of heart failure which was relieved by digitalis

PHARMACOLOGIC BASIS OF THERAPY

The pharmacodynamic actions of all digitalis materials are qualitatively the same they differ only in the parameters of action

Pharmacodynamic Actions —Digitalis has a number of actions The following have the more important clinical implications (1) intensification of vagal influence on the heart (2) increase of force of contraction of the ventricle, (3) depression of conduction (4) stimulation of myocardial automaticity (5) stimulation of the vomiting center (6) other central nervous system effects (7) diuretic action

VAGAL INFLUENCE ON THE HEART —Digitalis slows the heart through intensification of vagal influence on the sinus pacemaker Although there are other views this action may be presumed to be due to a lowering of the threshold of the sinus node to vagal tone It does not significantly slow a normal cardiac mechanism in man and has practical use only in the relief of auricular tachycardia This slowing action can sometimes be demonstrated in the normal dog with rapid acting digitalis materials such as acetyl strophanthidin

Slowing is usually the result of other digitalis actions When digitalis relieves heart failure this reduces the stimulus to cardiac acceleration and reflexly results in slowing of the sinus pacemaker In auricular fibrillation slowing may also be due to direct depression of A V conduction This applies only to the ventricular rate digitalis accelerates the auricular rate in auricular fibrillation

FORCE OF CONTRACTION —There is substantial evidence that digitalis increases the force of contraction of the ventricle, but this action cannot be demonstrated on normal muscle In the laboratory the isolated strip of cardiac muscle must first be fatigued at this point, digitalis markedly increases the strength of the contraction The same is true in man Digitalis has no perceptible effects on cardiovascular function of the normal heart On the other hand, there may be profound improvement in myocardial function in heart failure It is important clinically that digitalis cannot be expected to improve myocardial function unless it is deficient On the other hand in cases of congestive failure in which digitalis does exert this action the improvement in cardiodynamics produces a secondary effect on the kidney resulting in the classic diuresis after digitalis

DEPRESSION OF CONDUCTION —This action is therapeutic or toxic, depending largely on the situation in which it develops It is the basis of an important therapeutic effect in the treatment of auricular fibrillation In the Adams Stokes syndrome, digitalis may be used to fix heart block, thus to prevent syncopal attacks

ABSORPTION —There are the widest possible variations in the degree of ab-
rption of the various glycosides

Gastrointestinal Ouabain is not absorbed from the gastrointestinal tract Digi xin is practically completely absorbed from the intestinal tract It may be fairly ated that there is no other pure glycoside now available which is completely ab rbed The other glycosides lie between these extremes Acetyldigitoxin is prob bly only 60 per cent absorbed Digoxin is about half absorbed, while some, like edilanid, are probably only 10 to 20 per cent absorbed

Rectal Almost always this route is used only when the oral is not feasible No recise measurements have been made of the relative extent of absorption by this ute It has been assumed to approximate the oral in speed as well as extent

Intramuscular This route of administration is convenient and avoids the dan rs inherent in the intravenous route While it seems unquestionable that digitalis aterials are absorbed after intramuscular injection, there is little precise infor ation on the relative speed of development of action after this route of adminis ation It is generally assumed that absorption is more or less complete

It has been found that, after intramuscular injection, Lanoxin (digoxin) ef cts do not develop any more rapidly than after oral administration Much the me is true of digitoxin As matters stand, therefore, there seems to be no evi nce of an advantage in time in the intramuscular administration of digitalis aterials This route however, is available when oral rectal or intravenous ad inistration is not feasible

Intravenous The intravenous route of administration of digitalis materials may ll be considered here, because, though there are no problems of absorption into e blood stream, even by this route, there are issues of importance related to delay the development of effects As might be expected, by this route of administra on effects develop more rapidly than by any other It is noteworthy, however, at this difference is not invariably great enough to be of practical importance the case of digitoxin, for example, even after intravenous injection, there is a lay of about 6 to 8 hours before effects are fully developed, while the period for ll development of effects after oral administration is not much longer, about 8 to hours The difference between rates of development of action after the two utes of administration is more distinctive in the case of Lanoxin (digoxin) In case of some, such as acetyl strophanthidin and thevetin, effects come on almost tantaneously after intravenous injection These two, however, are not well sorbed from the gastrointestinal tract Effects from ouabain develop fully within out 90 minutes after intravenous injection—much the same as for Lanoxin

The reason for latency after intravenous injection is not established, it is prob le that it has to do either with some process of biotransformation which alters drug to the form which actually induces the typical digitalis actions or to some ocess of cellular absorption In any event, it is the period of latency which makes e digitalis more useful than another in the circumstance which indicates the ministration of a digitalis material by the intravenous route

The dangers incident to the intravenous injection of digitalis materials are not ndamentally different from those which complicate the administration of any other ug when the intravenous route is chosen The rapidly acting digitalis materials

n the other hand the emesis may interfere with the regimen of medication, while e exertions incident to vomiting may be dangerous Vomiting due to a local tion usually develops within half an hour after the oral administration of rela vely large doses It may be due to impurities in the preparation although the urified glycosides also can induce a local emetic action

The relatively pure glycosides simply because they contain less extraneous aterial are less likely to irritate the gastrointestinal tract, to induce nausea or omiting than the same glycosides in cruder form Thus 1 2 mg of digitoxin is ss likely to induce vomiting than an equivalent biologic dose of the pulverized af of *D gitalis purpurea* (1 2 Gm) This difference in irritant action is more kely to result in symptoms when large doses are used for digitalization than when nall doses are used for maintenance

While there are differences in the local emetic action of the purified glycosides hese have not been precisely evaluated but are probably not significant

Systemic Actions In so far as all digitalis glycosides have the same pharma ologic actions on the heart and the central nervous system their systemic toxic ctions are the same In each instance the development of systemic nausea or omiting xanthopsia or cardiac arrhythmias represent about the same relationship o the development of therapeutic effects That is to say, the therapeutic ratio is bout the same for all the glycosides Contrary statements will be found in the terature but here careful analysis will reveal either that the doses compared were ot biologically equal or that the ratio was developed on the bas s of local effects t is my opinion that there is no satisfactory evidence that any one digital s gly oside has a greater biologic tendency to induce cardiac arrhythmias or vomiting han the others

It is important that the action of digitalis on the vomiting center, which is so ignificant a warning may disappear with continued digitalization This may be hy serious poisoning is encountered more often in the patient taking digitalis daily han after the fairly rapidly ind iced initial d gitalization

The importance of serum and intracellular potassium in the development of ardiac arrhythmias is increasingly attracting attention The evidence is definite hat disturbances in rhythm due to digitalis are enhanced by reduction in intra ellular potassium This is not specific for any one glycoside but applies equally o all it is not a factor in the choice of digitalis materials On the other hand he indiscriminate treatment of all disturbances of cardiac rhythm in patients eceiving digitalis with potassium has met with utter failure

The recent report of Gubner and Kallman that based on the reciprocal rela ionship between blood calcium levels and digitalis toxicity systemic digitalis ntoxication may be treated by chelation of blood calcium is both interesting and encouraging and is now supported by the experience of others

Therapeutic Ratio Although others differ some vehemently it is my opinion hat there are no significant differences in the therapeutic ratios of the purified gly osides There are practical differences between mixtures and impure materials. These are largely proportionate to the amount of impurity which is administered with the glycoside These d fferences become relatively insignificant, however when the drug is given in small single doses for maintenance

INITIAL DIGITALIZATION —The average digitalizing dose has been the subject of acrimonious dispute In actual fact the term has many meanings because in different hands different therapeutic end points are used

I think the concept of Gold that 1 2 mg of digitoxin is the average single full digitalizing dose would benefit by some explanation Gold s data were obtained from patients with auricular fibrillation These patients were used because they are the most sensitive objective clinical indicators of digitalis action In the strict est sense, therefore the principle of dosage which he has set refers specifically to patients with auricular fibrillation although there is every reason to suppose that they apply to the use of digitalis in heart failure in general

Gold s dose was determined as the largest single dose which could be used with a negligible incidence of nausea Only 3 per cent suffered nausea or vomit ng and no patient in his large series had any disturbance of cardiac rhythm after a single dose of 1 2 mg of digitoxin When the dose was raised to 1 5 mg un toward effects rose to about 15 per cent, and with a 1 8 mg dose to about 33 per cent

It is my feeling that it is the use of the word full which stands in the way of the understanding and acceptance of Gold s dosage The 1 2 mg dose of digi toxin is by no means a full dose for most patients The dose of 1 2 mg is really a safe starting dose many patients require more a very few should get less In this sense it applies to all the situations in which digitoxin may be used

There would have been less confusion and perhaps more precision if the dose had been called a safe single initial digitalizing dose It is well to remember in this connection that 1 2 mg of digitoxin represents only 3 cat units This is bio logically equivalent to 0 3 mg of ouabain Few are fearful of injecting 0 5 mg of ouabain intravenously Security in this dosage of ouabain lies in the fact that it has been accepted that the full dose of ouabain is 1 mg Yet the physician who gives 5 cat units of ouabain intravenously without hesitation is reluctant to give 3 cat units of digitoxin by mouth I can explain this inconsistency only by the fact that the latter has been called a full dose, and we all hesitate to use a full dose at one time in fear that it may be excessive for sensitive patients

In any event the initial digitalizing dose should be the one which will provide as much digitalis effect in one dose as is possible without hazard In the case of digitoxin this happens to be 1 2 mg Dosage with other materials varies with their absolute potency The logical basis for the choice of a material for d gitalization is largely dependent on the urgency of the situation

Cumulation Method of Digitali ation The amount of d gitalis excreted is a relatively fixed percentage of the amount in the body so that when daily doses are given digitalis effects tend to cumulate and eventually full digitalization is achieved It is therefore possible to digitalize by the daily adm nistration of a small dose

It requires considerable trial before satisfactory adjustment of the daily dose is made It should be mentioned that the more rapidly eliminated the digitalis mate rial the more difficulty there is in d gitalization by this method Here it is that digitoxin is by all odds the drug of preference It should be stated however that since digitalis leaf provides its effects principally through its digitoxin content it also has these advantages and that given in the relatively smaller doses required

provide a decided convenience in producing their effects within a period of time in which it is practical to keep the patient under constant careful supervision They are also fortunate as a group of drugs in having correspondingly rapid elimination characteristics so that in the event of overdigitalization this effect is more rapidly taken care of by time alone.

Development of Effects —There are great differences in the rate of the development of the effects of the digitalis materials There are, on the one hand, glycosidal materials like thevetin and acetyl strophanthidin which produce almost instantaneous effects so that even before the intravenous injection is completed the effects are seen and within 15 minutes are fully developed At the other extreme is digitoxin which requires perhaps 3 hours for perceptible effects and 6 to 8 hours for full development after an intravenous dose Between these extremes lie digoxin and ouabain which require about 30 minutes for the appearance of significant effects and close to an hour and a half for full effects after the intravenous injection of a dose These statements relate to intravenous injections only When they are given by the oral route, the time required for absorption slows the development of effects while incomplete absorption reduces the peak of effects thereby tending to reduce the difference in the rate of development of full effects of different glycosides, e g , digitoxin and digoxin

Elimination —Elimination of digitalis materials can be measured only in terms of biologic effects it is a highly individualized characteristic Thus virtually all the effects of a single dose of acetyl strophanthidin disappear within an hour or so after an injection while the effects of an equal biologic dose of digitoxin may persist for as long as 2 weeks Between these two extremes are drugs like Lanoxin (digoxin) and ouabain, the greater part of their effects are eliminated within 24 hours It is of practical importance that while oral administration tends to reduce the difference in the rate of development of effects of different glycosides it has relatively little influence on the difference in the relative rates of the dissipation of effects

Curve of Action —From the foregoing it is clear that the curve of action of digitalis materials tends to be symmetrical, those which develop their actions with great speed are speedily eliminated and those which develop their actions slowly are slowly eliminated Obviously this affects the choice of the best drug for rapid digitalization and the best for maintenance

Dosage —The principles of dosage laid down by Withering still obtain " let it be continued until it either acts on the kidneys the stomach the pul e, or

se effects'

Whether

of digitalis

depends on the use for which it is intended the nature of the effect sought and the amount found to be necessary to produce it Dosage depends on the specific pharmacologic aim in auricular flutter it is the development of auricular fibrillation in heart block it is an increase in idioventricular rate in sinus tachycardia it is intensification of vagal tone, in auricular fibrillation it is slowing of the ventricular rate and in heart failure with a normal sinus rhythm it is increase in force of ventricular contraction

INITIAL DIGITALIZATION —The "average digitalizing dose" has been the subject of acrimonious dispute In actual fact, the term has many meanings because in different hands different therapeutic end points are used

I think the concept of Gold that 1 2 mg of digitoxin is the "average single full digitalizing dose" would benefit by some explanation Gold's data were obtained from patients with auricular fibrillation These patients were used because they are the most sensitive objective clinical indicators of digitalis action In the strictest sense, therefore, the principle of dosage which he has set refers specifically to patients with auricular fibrillation, although there is every reason to suppose that they apply to the use of digitalis in heart failure in general

Gold's dose was determined as the largest single dose which could be used with a negligible incidence of nausea Only 3 per cent suffered nausea or vomiting and no patient in his large series had any disturbance of cardiac rhythm after a single dose of 1 2 mg of digitoxin When the dose was raised to 1 5 mg untoward effects rose to about 15 per cent, and, with a 1 8 mg dose, to about 33 per cent

It is my feeling that it is the use of the word 'full' which stands in the way of the understanding and acceptance of Gold's dosage The 1 2 mg dose of digitoxin is by no means a 'full' dose for most patients The dose of 1 2 mg is really a safe starting dose, many patients require more, a very few should get less In this sense it applies to all the situations in which digitoxin may be used

There would have been less confusion and perhaps more precision if the dose had been called a "safe single initial digitalizing dose" It is well to remember in this connection that 1 2 mg of digitoxin represents only 3 cat units This is biologically equivalent to 0 3 mg of ouabain Few are fearful of injecting 0 5 mg of ouabain intravenously Security in this dosage of ouabain lies in the fact that it has been accepted that the 'full dose of ouabain is 1 mg Yet the physician who gives 5 cat units of ouabain intravenously without hesitation is reluctant to give 3 cat units of digitoxin by mouth I can explain this inconsistency only by the fact that the latter has been called a "full' dose, and we all hesitate to use a 'full' dose at one time in fear that it may be excessive for sensitive patients

In any event, the initial digitalizing dose should be the one which will provide as much digitalis effect in one dose as is possible without hazard In the case of digitoxin this happens to be 1 2 mg Dosage with other materials varies with their absolute potency The logical basis for the choice of a material for digitalization is largely dependent on the urgency of the situation

Cumulation Method of Digitalization The amount of digitalis excreted is a relatively fixed percentage of the amount in the body so that, when daily doses are given, digitalis effects tend to cumulate and eventually full digitalization is achieved It is therefore possible to digitalize by the daily administration of a small dose

It requires considerable trial before satisfactory adjustment of the daily dose is made It should be mentioned that the more rapidly eliminated the digitalis material, the more difficulty there is in digitalization by this method Here it is that digitoxin is by all odds the drug of preference It should be stated, however, that since digitalis leaf provides its effects principally through its digitoxin content, it also has these advantages and that given in the relatively smaller doses required

by this method of digitalization the incidence of locally induced na likely to be higher than with digitoxin The physician is warned here possible by this method of administration to cumulate to toxic levels. when the amount excreted daily equals the daily dose, there is no furth lation and the biologic effect is stabilized. This dose then becomes the nance dose.

MAINTENANCE.—Maintenance implies even and sustained digitalis Often this means the regimen for the remainder of the patient's life Satis maintenance is therefore a major therapeutic accomplishment Unfortur there is no universal maintenance dose for any digitalis material If effects a be maintained the rate of administration must equal the rate of elimination. maintenance dose must therefore be adjusted in such a way that the biologic ef is sustained This requires a manipulation of dosage which takes into accou the range of individual variation of the elimination as well as the absorption the digitalis material It is not surprising therefore that often maintenance re quires more attention and is more troublesome than the initial digitalization. The latter can often be accomplished in a day or so the former may take weeks

The maintenance dose also varies with digitalis materials depending on elimi nation as well as potency Thus in the case of acetyl strophanthidin which is al most completely eliminated in an hour or so doses close to the initial digitalizing dose have to be given every few hours while in the case of digitoxin from one sixth to one twelfth of the initial dose may be all that is necessary Between these ex tremes lies digoxin about one-third of the initial dose being required to maintain effect In the case of the relatively rapidly eliminated drugs the effect is not maintained on a completely even keel however but tends toward crests and troughs during the course of the day Because of this it has been suggested recently that these materials are better administered 3 times a day whereas a level effect may be obtained with a single dose of digitoxin. For these reasons once the dose is established the slowly eliminated digitoxin is the drug of choice for maintenance

TOLERANCE.—Pharmacologic tolerance of the heart muscle to digitalis does not develop Patients who once did well on digitalis often do not continue to respond as well after the long continued use of the same dose but here progression of the heart disease is usually the cause In some of these cases, increase in the dose of digitalis may be helpful but if the patient was well digitalized initially increase in dosage is rarely helpful and may cause trouble

DIGITALIS TOLERANCE TEST.—A test utilizing the principle of biologic titration has been introduced to determine whether a patient will react adversely to a rela tively large dose of digitalis such as would be used for rapid digitalization This is an important problem at all times, but it is especially so when it is not known whether a patient has had digitalis recently or when there is the question of how much of previously administered digitalis has not yet been eliminated.

In the test the rapid acting glycosidal material acetyl strophanthidin is given. the effect on the electrocardiogram is observed Intolerance to digitalis is indi by the development of electrocardiographic evidence of toxicity The defense of the method lies in the rapid elimination of acetyl s If toxic effects develop they may be expected to disappe

therefore, without disaster This has not always proved to be the case, and in two series totaling about 40 patients there were two fatalities as a result of the test I, for one, could never defend so hazardous a test for use in a problem which can usually be solved with care and patience

A more recent test depending on the reciprocal relationship between blood calcium levels and the electrocardiographic effects of digitalis is discussed on page 798 Here injections of calcium gluconate sufficient to elevate blood calcium levels are used to establish the presence or absence of digitalis action Toxic effects may be overcome by the intravenous injection of chelating agents to reduce blood calcium levels

Summary —Much pointless argument has developed about the choice of digitalis materials while differences between members of other pharmacologic groups have not engendered as much heat

There are some 60 barbiturate drugs available, yet only the manufacturers seem to have strong personal feelings about their choice It is recognized that the therapeutic ratios of all the members of the barbiturates are about the same and no supportable argument can be presented for superiority on that basis The only meaningful differences lie in the parameters of their action some are more slow to develop their actions than others some more quick to eliminate theirs than others These differences make one a useful anesthetic, another a good sedative or hypnotic

The analogy of barbiturates with the digitalis materials suggests the basis for choice The rapid acting digitalis materials are clearly more desirable for parenteral use in urgent situations than the slow acting ones On the other hand the slowly eliminated ones are clearly preferable for maintenance of effects Where there is danger of overdigitalization the more rapidly eliminated digitalis materials provide a greater degree of safety in rapid dissipation of possible excessive effects

The cruder preparations have only the advantage of cost This differential has been considerably reduced by improvements in manufacturing processes so that the small difference in cost may now be defensible in terms of convenience and decrease in local irritant action But it should be remembered that there is no digitalis action on the heart which cannot be developed just as well with the crude preparation as with the same glycoside with the impurities removed

THE SEVERAL DRUGS

Crude Digitalis Materials—Only tablets made of the pulverized and hydroalcoholic extracts of the leaf (i e, *tinctures*) of *Digitalis purpurea* are still in use in this country The chief if not the only, glycoside in these preparations which is absorbed from the gastrointestinal tract is digitoxin They might well be considered merely crude preparations of digitoxin The use of these crude preparations is declining

Purified Digitalis Glycosides—These are represented by relatively pure crystalline and amorphous glycosides and mixtures of glycosides The materials now in use are extracted from *Digitalis purpurea Digitalis lanata Strophanthus gratus Strophanthus kombé*, and squill

Ouabain—For many years ouabain was the standard against which all digitalis

by this method of digitalization, the incidence of locally induced nausea is not likely to be higher than with digitoxin. The physician is warned here that it is possible by this method of administration to cumulate to toxic levels. However, when the amount excreted daily equals the daily dose, there is no further cumulation and the biologic effect is stabilized. This dose then becomes the maintenance dose.

MAINTENANCE.—Maintenance implies even and sustained digitalis action. Often this means the regimen for the remainder of the patient's life. Satisfactory maintenance is therefore a major therapeutic accomplishment. Unfortunately, there is no universal maintenance dose for any digitalis material. If effects are to be maintained, the rate of administration must equal the rate of elimination. The maintenance dose must therefore be adjusted in such a way that the biologic effect is sustained. This requires a manipulation of dosage which takes into account the range of individual variation of the elimination as well as the absorption of the digitalis material. It is not surprising, therefore, that often maintenance requires more attention and is more troublesome than the initial digitalization. The latter can often be accomplished in a day or so, the former may take weeks.

The maintenance dose also varies with digitalis materials, depending on elimination as well as potency. Thus in the case of acetyl strophanthidin which is almost completely eliminated in an hour or so, doses close to the initial digitalizing dose have to be given every few hours, while in the case of digitoxin from one sixth to one twelfth of the initial dose may be all that is necessary. Between these extremes lies digoxin, about one third of the initial dose being required to maintain effect. In the case of the relatively rapidly eliminated drugs, the effect is not maintained on a completely even keel, however, but tends toward crests and troughs during the course of the day. Because of this, it has been suggested recently that these materials are better administered 3 times a day, whereas a level effect may be obtained with a single dose of digitoxin. For these reasons, once the dose is established, the slowly eliminated digitoxin is the drug of choice for maintenance.

TOLERANCE.—Pharmacologic tolerance of the heart muscle to digitalis does not develop. Patients who once did well on digitalis often do not continue to respond as well after the long continued use of the same dose, but here progression of the heart disease is usually the cause. In some of these cases, increase in the dose of digitalis may be helpful, but if the patient was well digitalized initially, increase in dosage is rarely helpful and may cause trouble.

DIGITALIS TOLERANCE TEST.—A test utilizing the principle of biologic titration has been introduced to determine whether a patient will react adversely to a relatively large dose of digitalis such as would be used for rapid digitalization. This is an important problem at all times, but it is especially so when it is not known whether a patient has had digitalis recently or when there is the question of how [illegible]

cated by the development of electrocardiographic evidence of toxicity.

The defense of the method lies in the rapid elimination of acetyl strophanthidin. If toxic effects develop, they may be expected to disappear promptly and,

Digoxin The similarity in the spelling of digoxin and digitoxin has led to some confusion *The recently introduced* proprietary name, Lanoxin, therefore has an advantage

Lanoxin has a curve of action which may be somewhat slower but which approximates that of ouabain *Compared with ouabain, it has the drawbacks of its* slightly slower curve of action Used orally for maintenance, effects tend to be uneven with wide variations in intensity during and between the doses

It is not soluble in water Recently, however, a *new satisfactory parenteral* preparation has been made available

Intramuscular injection of Lanoxin provides no advantage in speed of action over the oral administration Lanoxin is poorly absorbed from the intestinal tract, about 50 per cent of the amount administered is absorbed This must be taken into account in dosage regimens

Acetyldigitoxin This glycosidal material resembles Lanoxin more than digitoxin in its curve of action About two-thirds of the dose administered by mouth is absorbed It is somewhat more slowly eliminated than digoxin This is no longer a new glycoside, special merits have not yet been demonstrated Its present position is that of just another digitalis material with a moderately rapid curve of action and incomplete absorption

Digilanid This is a mixture of the lanatoside glycosides in *Digitalis lanata,* lanatoside A, lanatoside B, and lanatoside C The curve of action of this preparation closely simulates that of digoxin It is very poorly absorbed, from 10 to 20 per cent of the oral doses being absorbed from the gastrointestinal tract

Lanatoside C This glycoside (*Cedilanid*) *resembles Lanoxin closely in curve* of action and therefore provides no advantage over it Only about 10 per cent of an oral dose is absorbed

Deslanoside This (*Cedilanid D*) *is still another lanata* glycoside which has a curve of action similar to Lanoxin It is a very recent introduction, and if it has any advantages over Lanoxin, they have not yet been established From the information already at hand concerning its actions, there seems to be no reason to suppose that it should have unique virtues It is available only as a parenteral preparation

SQUILL —Squill was used in medicine as a diuretic even before Withering introduced digitalis Although still used in this country, squill preparations have given way to digitalis preparations, perhaps largely because its parameters of action do not offer any unique advantage

Scillaren This is a mixture of scillaren A and scillaren *B* *Its curve of action* resembles that of digoxin It may be administered by mouth but it is poorly absorbed from the gastrointestinal tract

Scillaren B This is a purified gycoside *for intravenous injection* The material is made up in a strongly alcoholic solution and further dilution is the safer procedure No advantage over any of the other glycosides with an intermediary *speed of action has been established*

Urginin This is a mixture of two squill glycosides urginin A and urginin B There are no published reports that this is digitalis material with special virtues and as a result it is very little used today

materials were measured It is the most potent of all digitalis glycosides 0 1 mg is equivalent to 1 cat unit 0 5 to 1 mg is a full digitalizing dose

It is not absorbed at all from the gastrointestinal tract and is used intravenously Its curve of action is relatively rapid significant effects appearing within 30 minutes of intravenous injection and being fully developed within about 90 minutes Within 24 hours most of the effects disappear

It is relatively soluble and, of the commonly used parenteral materials it is the only one of which a full digitalizing dose can be dissolved in a small amount of water or saline

As matters stand it is usually the digitalis material of choice where rapid effects by intravenous injection are desired

STROPHANTHIN —This usually refers to *Strophanthus kombe* *Strophanthus gratus* being the source of ouabain Its curve of action is virtually identical with ouabain Since it is a somewhat variable mixture of glycosides, its potency is equally variable As a result and also perhaps because there is no need for more ouabain like materials it is little used

ACETYL STROPHANTHIDIN —This is one of the most rapidly acting digitalis glycosides It is given intravenously Effects begin almost instantaneously and within 15 minutes are fully developed They disappear equally rapidly This fleeting type of action is suited for emergencies after which it is followed by a more persistent glycoside It is also used for arrhythmias, in which, once the effect is developed persistence is not required Diuretic and slowing actions have been demonstrated but these are not of practical value It has been used in a hazardous test to determine digitalis tolerance Unfortunately, it is not available on the commercial drug market

THEVETIN —This glycoside has a curve of action and uses virtually identical with acetyl strophanthidin It is not available on the commercial drug market

DIGITALIS PURPUREA GLYCOSIDES —

Digitoxin This glycoside develops its effects more slowly than any other and is excreted more slowly Given orally its advantages lie in its complete absorption from the gastrointestinal tract lack of gastrointestinal distress and the fact that once the maintenance dose is adjusted effects may be maintained for years without difficulty

The parenteral preparations are not so outstanding The time required for effects to develop when they are urgently needed and for them to disappear when they are excessive constitutes its major disadvantage It is also highly insoluble and intravenous preparations may contain large amounts of alcohol Unless well diluted these solutions may be irritant More recently intravenous preparations have been made available which are more satisfactory from the physical point of view An intramuscular preparation is also available but its curve of action is not superior to that after oral administration

Gitalin This is an amorphous glycoside of the digitalis leaf which is poorly absorbed from the intestinal tract but is otherwise satisfactory and is favored by some experts There has recently been a strong effort to revive its use

DIGITALIS LANATA GLYCOSIDES —Digitoxin may also be obtained from *Digitalis lanata* but it is no different from the digitoxin obtained from *Digitalis purpurea*

Since the digitalis materials are qualitatively the same and their therapeutic ratios are identical, the basis for their choice lies in the nature of local irritant action in the gastrointestinal tract (if they are given orally) and in their parameters of action

So far as local irritant action is concerned, the problem is minimal with the pure material In general, it is more important in digitalization than in maintenance

For urgent situations, where only fleeting effects are desired, and where there is danger of overdigitalization, the materials with the more rapid curves of action are clearly the more desirable For such purposes there is the almost instantaneous effect of acetyl strophanthidin and the intermediary curve of ouabain and a large number of *lanata* and squill glycosides A relatively prolonged curve of action is best suited for the maintenance of even effects Here digitoxin (or even digitalis leaf) is the drug of choice

The dose of a digitalis material depends upon which of the several digitalis effects is sought on cardiac contraction in heart failure, on conduction in auricular fibrillation, on auricular rhythmicity in auricular flutter, on ventricular automaticity in heart block, on vagal tone in sinus tachycardia

RATIONAL BASIS FOR NEW DIGITALIS MATERIALS

On the basis of our present knowledge of an extremely large number of natural digitalis materials, it seems unlikely that exploration of the remaining digitalis glycosides will uncover quantitatively superior or qualitatively more desirable pharmacologic actions Should such differences be developed a reassessment of the digitalis glycosides would be necessary

Differences in therapeutic ratio seem improbable because cardiotoxicity, the greatest danger from digitalis by overdosage, is an extension of the therapeutic action on the heart and, therefore, seems inseparable from it It must be admitted however that a drug with such a segregation of action would have a clear advantage over those now available Digitalis materials are far more likely to have differences in parameters of action

Local irritant actions seem to have been reduced to the null point by the purification of glycosides Systemic emesis is a useful sign of impending toxicity and a glycoside without this might be more dangerous

Perhaps the most useful addition to what we already have would be an intramuscular preparation with a significantly more rapid curve of action than that of oral preparations or an oral preparation with a truly rapidly developing curve of action These would provide a much needed practical intermediate between intravenous and oral administration as it now stands

THE CHOICE OF DRUGS FOR CARDIAC ARRHYTHMIAS

INTRODUCTION

Despite effective drugs for their relief, cardiac arrhythmias remain among the less successfully treated complaints The choice of the drug is not so common a cause of failure as the choice of dosage Another reason for failure in the treat

CONVALLARIA —This digitalis material is barely absorbed from the gastrointestinal tract and since no attribute of its action by any other route has been demonstrated to be superior, it is not in common use

Choice of a Digitalis Material —Two digitalis glycosides stand out

Ouabain is the rapid acting material of choice It is a standard material with which there is great experience No material now available commercially has a more rapid curve of action It cannot be used orally But this disadvantage is more apparent than real since if digitalis action is urgently needed, the oral route is not the route of choice From this standpoint glycosides like Lanoxin with curves of action similar to, or slower than ouabain have little to offer

Digitoxin is the drug of choice among the slow acting digitalis materials Once developed level maintenance is more likely with it than with any other digitalis material It is the drug par excellence for oral use being completely absorbed The parenteral preparation appears useful only when the oral route is not feasible

The extremely rapidly acting materials acetyl strophanthidin and thevetin, are not commercially available The others have less clearly defined spheres of special usefulness

Sympathomimetic Amines —The ionotropic effect of epinephrine and related drugs to increase the contractile force of the myocardium which can be easily demonstrated in the isolated cat papillary muscle has been suggested as an added attraction of these drugs, especially norepinephrine (Levophed), methoxamine (Vasoxyl) and mephentermine (Wyamine), when they are used for their effects on blood pressure in patients with shock and congestive heart failure What such a hope fails to take into account is the fact that while digitalis increases the force of cardiac contraction in the case of *failing* heart the congeners of epinephrine stimulate the force of contraction of the *normal* myocardium There is in fact, no substantial clinical evidence that the ionotropic action of this series of drugs on the myocardium is of any value in the relief or prevention of congestive heart failure

Methamoctol Unless further investigation proves that this member of the sympathomimetic amine series is an exception to the rule all that has been said above applies to methamoctol (Aranthol)

DESIGN FOR THE USE OF DIGITALIS MATERIALS

I was impressed on reading through Withering's monograph on *The Foxglove* that he reported a higher order of success in the treatment of dropsy with his crude preparations than is usually obtained at the hands of most clinicians working 170 *years later with better standardized and more highly purified materials* Withering also reported a much higher incidence of toxic effects—about 15 per cent of his 163 cases It may have been even higher since many of his reports are fragmentary I suggest that there is a connection between the high order of success and the high incidence of reactions Withering pushed the drug until satisfactory effects or untoward effects developed He followed his adage—' let it be continued until it either acts on the kidneys the stomach, the pulse or the bowel '

In 170 years no better way has been devised to squeeze the most out of digitalis

are often triggered by anxieties and by sudden as well as continued efforts The patient is protected from them in the hospital, but when he is sent home he is no longer so well guarded The anxieties of family life, the understandable attempts to be less of a burden at home, the question of earning a living, the stress of the job—any one or any combination of these may be enough to trigger an attack A disturbance in cardiac mechanism may therefore require more intensive therapy for prevention than for relief In my own experience, satisfactory results with prophylactic therapy usually have been obtained only when dosages at least as large as those used in treatment were applied, or where practical arrangements could be made to alter home and work situations

Disorders of Rhythm —

DISORDERS OF CARDIAC RHYTHM OF UNDETERMINED NATURE —Cardiac arrhythmias which do not cause symptoms usually can wait for precise identification The urgency of a disorder in rhythm is determined by clinical considerations, the general condition of the patient, observations on cardiovascular and respiratory function and the basic cardiac disease Cardiac arrhythmias which develop during acute or healing phases of infarction are far more likely to have serious implications than those which develop in less consequential heart disease Arrhythmias developing during anesthesia often disappear afterward and in the case of a normal heart usually require no treatment

The most serious danger in the treatment of unidentified arrhythmias is the abolition of idioventricular rhythmicity in the patient with heart block Such a drug action can only be followed by cardiac standstill Since this possibility must be considered in every case of undiagnosed arrhythmia, the therapeutic aim at this stage must be to slow the rhythm, not to abolish it

With this admonition in mind, quinidine or Pronestyl may be used in undiagnosed cardiac arrhythmias The precautions outlined below for the treatment of ventricular tachycardia should be followed The choice between the two depends largely on the mode of administration Pronestyl is preferred for parenteral administration

SUPRAVENTRICULAR RHYTHMS —Supraventricular rhythms are usually less urgent than idioventricular rhythms and, while auricular flutter and fibrillation are often serious matters, even these generally permit time for thoughtful consideration Many supraventricular rhythms, particularly the paroxysmal types require no treatment beyond that demanded by the physical discomforts of the patient

Sinus Arrhythmia Sinus arrhythmia is a physiologic response and in itself is never an indication for treatment

Premature Contractions Premature auricular contractions never threaten cardiac function and are of little prognostic import When they impinge upon the patient's consciousness, it may be impossible to distract him from them, and in such a situation, treatment may be necessary

Effective prevention of premature contractions through the continued use of cardiac depressants such as Pronestyl or quinidine requires large doses Often this implies more trouble than the disturbance warrants Quinidine is usually the preferred drug Digitalis is effective only when cardiac failure is the cause of the

ment of cardiac arrhythmias is the belief that prophylaxis is simpler than treatment

The useful drugs are few and their choice is fairly obvious a more difficult decision is the choice between treatment and no treatment The decision to treat is important not only because it may become an involved procedure, but also because it directs the patient s attention to his heartbeat and makes success imperative where it may be a matter of no importance from the point of view of cardiodynamics Cardiac arrhythmias often do not require treatment Rapid or irregular heart action is not dangerous to the normal heart and does not invariably interfere with cardiodynamics Tachycardias are a threat to the diseased heart in proportion to the extent of myocardial disease, the ventricular rate, and whether the ventricular contraction is well enough organized to expel its contents efficiently The cause of the disturbance is often a greater threat to the patient than the disturbance itself

Until recently relatively few drugs mainly digitalis and quinidine, were used for disturbances in cardiac rhythm More recently Pronestyl achieved a firm position In the last year or two however a large number of reports on less well understood therapies have been examined Among these mephentermine is most prominent, but other sympathomimetic amines chloroquine, and several tranquilizers have also attracted attention At this time the evidence in favor of the last two is not convincing whereas interest in the former is firm at the moment

CLINICAL CONSIDERATIONS

The obvious procedure in the treatment of cardiac arrhythmias is to discover the cause and to eliminate it In so far as some disturbances in cardiac rhythm have such definitive causes as hyperthyroidism or intoxication, there is a realistic basis for an etiologic approach On the other hand, there are cardiac arrhythmias which cannot be treated etiologically because the cause is unknown where it is known, there is no specific treatment or heroic measures must be applied before the information necessary for etiologic treatment can be obtained With the importance of etiologic relief well in mind this discussion will consider methods of alleviating cardiac arrhythmias by agents which affect the rhythmic mechanism directly, not its cause

Precise definition of the disturbance in rhythm is most useful in decisions on drugs and dosage schedules Unfortunately, this is not always possible There are however, instances in which because precise electrocardiographic diagnosis cannot be made or cannot be made soon enough therapy must be instituted without its help

Prophylaxis Versus Treatment—Prevention has obvious advantages over treatment When there is a history of repeated paroxysms of premature ventricular contractions which may be interpreted as precursors of ventricular tachycardia nothing is more to be desired than effective prophylaxis

Patients with cardiac arrhythmias may respond promptly and easily to treatment in the hospital, and therefore it is disturbing to the physician that, when they are returned to their homes prophylactic regimens of reduced dosage are often unsuccessful The difficulties which attend the implementation of prophylaxis arise from the fallacy that prophylaxis is simpler than treatment Arrhythmias

rhythm in about 60 per cent of cases with auricular fibrillation In the majo however, the auricular fibrillation soon returns In thyrotoxicosis or other int cations causing auricular fibrillation, the normal rhythm tends to persist afte restoration, while in cases of auricular fibrillation due to rheumatic and arterio rotic heart disease and especially those with cardiac failure, the results are likel be short lived

Digitalis can almost always be counted upon to slow the ventricular rate auricular fibrillation, this is perhaps the most dependable of all its therape effects It may decrease the ventricular rate through improvement of myocar function, diminishing the reflex stimulation to acceleration, but even when it f to improve myocardial function, continued use of digitalis slows the heart by other action—direct depression of auriculoventricular conduction Excessive d talis dosage produces exceedingly slow ventricular rates and coupling

Statements that strophanthin may be used to restore a normal sinus rhyt by a direct action must be questioned There is no pharmacologic basis for such direct action of any digitalis material on the auricle and, in addition, in the stud reported, it is likely that the successful cases had paroxysmal auricular fibrillat and that the resumption of a normal rhythm was spontaneous and not the res of the action of the digitalis material

In the use of quinidine and Pronestyl in auricular fibrillation, the ventricul rate increases as the effects develop In the series of changes, the auricular ra may briefly change to a flutter before the normal rhythm appears The grav danger in restoring a normal rhythm lies in discharging emboli from previou stagnant auricular appendages at the moment of the shift from auricular fibrillati to a normal rhythm This is not a danger inherent in quinidine or Pronestyl b rather one which is inherent in auricular fibrillation and which exists when an drug or circumstance causes a previously inactive auricular appendage to co tract The cause, therefore, lies in the success in restoring a normal sinus rhyth in a patient with auricular fibrillation Any blame for such an accident lies n with the drug but with the decision to restore a normal rhythm

Digitalis is the drug of choice in all cases with long standing auricular fibri lation auricular fibrillation with congestive heart failure or advanced heart diseas Quinidine is the preferred drug when there is little danger of embolization mino heart disease, and small likelihood of recurrence of the auricular fibrillation

IDIOVENTRICULAR RHYTHMS —

Auriculoventricular Dissociation Failure of the ventricle to respond to auricu lar impulses does not in itself embarrass cardiac function Cardiac function can proceed satisfactorily without auricular contractions or synchronism between auricle and ventricle, viz, the lack of circulatory embarrassment in many cases of heart block and in cases of slow auricular fibrillation

Auriculoventricular dissociation is not an indication for therapy, nor will its restoration be certain to provide the answer when there is cardiodynamic embar rassment The more important determinants of treatment are the nature of the basic heart disease, the nature of the idioventricular rhythm, and the development f ... ms as a conseq ence of the abnormal cardiac mechanism

disturbance Since digitalis is always indicated for heart failure, it is automatically used in the cases with premature auricular contractions in which it may be useful

When the premature contractions are associated with anxiety states, sedation may be effective

Sinus Tachycardia Sinus tachycardia is the most common form of rapid heart action Often it is an entirely normal physiologic response to cortical impulses, fever, and noncardiac disease as well as disease of the heart and congestive failure The most consistent relief comes from the removal of the cause Quinidine and Pronestyl are rarely effective in sinus tachycardia, to be effective, doses larger than those most physicians would be willing to give are usually necessary Where the sinus tachycardia is a physiologic response to a disease, it is unlikely that these agents will be effective in any dosage

Auricular Tachycardia When adequate dosage is employed, quinidine is more useful in auricular tachycardia than in sinus tachycardia The difference in the relative utility probably lies in the fact that in auricular tachycardia an abnormal focus is the pacemaker

Vagal stimulation through eyeball or carotid sinus pressure can be successful, but it frequently fails Here the action of digitalis to sensitize the sinus node to vagal impulses is effective though rarely used After a relatively large dose of a digitalis material, preferably a relatively rapid acting one such as acetyl strophanthidin or ouabain, eyeball or carotid sinus pressure may slow the rapid rate where previously it failed This maneuver is often a more practical approach to the problem than the use of quinidine or Pronestyl Emetics may also be used to induce intense vagal stimulation

Nodal Tachycardia Although the clinical features of the treatment of nodal tachycardia are similar to those of auricular tachycardia, the former is more resistant to quinidine and Pronestyl Digitalis is of no value

Auricular Flutter Auricular flutter is commonly paroxysmal, often it is replaced by auricular fibrillation

The action of digitalis in auricular flutter is unique It is given in doses which change the flutter to a fibrillation at which point it is discontinued and its effects are permitted to dissipate In approximately half of the cases, as digitalis effects wear off a normal rhythm appears, in the other half, the flutter reappears or the fibrillation persists Digitalis is not useful for prophylaxis, therefore Since rapidity in development and dissipation of effects are desired for treatment, a rapid acting material such as ouabain, is the drug of choice

Quinidine and Pronestyl may also be used here, much as in auricular fibrillation The former is more generally chosen

Auricular Fibrillation Digitalis, quinidine and Pronestyl are used in auricular fibrillation, but the pharmacologic aims are different quinidine and Pronestyl are used to abolish the fibrillation and to restore a normal rhythm, while digitalis is used only after it has been decided to accept the cardiac arrhythmia and to treat by slowing the ventricular rate

Quinidine is more firmly established than Pronestyl in this condition, although the indications are that there is little to choose between them. The experience with quinidine is considerably greater and indicates that it will restore a normal

at a rate of 40 per minute does not mean that there is seriously reduced cardiac output for as the ventricular rate decreases the stroke volume tends to increase There is of course, a critical rate below which increased stroke output cannot make up for decreased cardiac rate and when the cardiac rate falls below it cardiac output becomes *inadequate*

The dramatic episodes of the Adams Stokes syndrome in which brief periods of unconsciousness and sometimes even convulsions develop always merit attention *It is common to explain these* episodes as periods of ventricular asystole due to a latency between the lapse of supraventricular control and the appearance of the idioventricular pacemaker *There is also evidence that this period of latency is* related to the rate at which the ventricle has been previously driven by the auricle—the faster the supraventricular rhythm, the longer the period of latency In many cases of intermittent heart block, the auricular rhythm is not excessive and therefore, there is not likely to be a prolonged period of ventricular asystole In such cases Adams Stokes episodes may not develop at all and if they do they are likely to be both brief and of moderate intensity

It is less commonly recognized that Adams Stokes episodes develop during periods of exceedingly slow idioventricular rates, sometimes 20 or less and during *brief paroxysms of ventricular tachycardia and of ventricular fibrillation The pulse of the unconscious patient with heart block does not give the information* necessary to distinguish between the latter two Often the stethoscope is equally uninformative There is no blood pressure in asystole and there is virtually none in ventricular fibrillation On the other hand it is well to remember that in ventricular tachycardia the exceedingly rapid ventricular rate reduces the amplitude of the pulse so that although mean blood pressure may be substantial it is not detectable by the usual method, which depends on a distinction between systolic and diastolic pressures

Isuprel is perhaps the most effective of the agents used in *heart block to in*crease the rhythmicity of the heart Other sympathomimetic amines are less *effective and some may be dangerous*

Ventricular Asystole Ventricular standstill can hardly be called an arrhythmia Therapy must be directed to the ventricle Isuprel is the drug of choice Intracardiac injection is the only effective route of administration of drugs The needle puncture itself may provide useful stimulation of the myocardium In attacks which develop in the hospital, the application of the external electrical *cardiac* pacemaker may be effective Vigorous direct manual cardiac massage may be useful Recently sodium lactate *has been suggested but further trial* with this agent is necessary

INTOXICATIONS —*Arrhythmias due to intoxication* comprise a special etiologic category Except for ventricular fibrillation even exceedingly rapid disturbances in rhythm are not so urgent as when they are the result of heart disease

Cardiac arrhythmias induced by intoxication vary considerably depending on circumstances the intoxicant and the presence of heart disease If the intoxicant is removed or treated specifically the arrhythmia will usually *disappear When it* does not it generally responds favorably to drug therapy Where life is not threatened by *the disturbance in rhythm there is* ample time for waiting for the

Premature Ventricular Contractions Premature contractions of the ventricle do not require therapy per se In some instances however, premature ventricular contraction beats may be precursors of the far more serious ventricular tachycardia, and where such a possibility exists their presence poses the problem of prophylactic therapy The decision has to be made on clinical grounds and if it is believed that there is such a danger the use of drugs is indicated Quinidine and Pronestyl are effective here while digitalis is not In patients with cardiac failure digitalis should be used unless there is clear and certain evidence that the premature contractions are an evidence of digitalis intoxication

Ventricular Tachycardia Ventricular tachycardia is one of the urgent cardiac arrhythmias and demands attention the moment it is suspected or even anticipated Serious heart disease is almost invariably the basis of the disturbance and here the rapid rate may be too much for the diseased myocardium

Grave dangers are inherent in both the existence and the abolition of the rhythm The possibility of heart block is of critical importance for it determines whether the abolition of the rhythm will be followed by a normal sinus rhythm or cardiac standstill Often the electrocardiographic picture is so bizarre that this critical question cannot be answered As long as the possibility exists the therapeutic aim must be to slow the ventricular rate and not to obliterate the ectopic rhythm Here decrease in rate from 200 to 150 is a significant therapeutic accomplishment and the therapeutist should be satisfied with it until he learns more When the cardiac rate falls P waves representing sinus activity may appear in the electrocardiogram If the electrocardiogram indicates that the auricular rate exceeds the idioventricular rate it is clear that there is heart block and it would be fatal to abolish the ventricle If the reverse is the case it is safe to proceed with the quinidine or Pronestyl but even so increase in dosage should be gradual

As with auricular fibrillation, the danger of catastrophe is inherent in the disturbance and not in the drug Any substitute for quinidine or Pronestyl which abolishes a ventricular tachycardia is equally capable of leaving the heart without a pacemaker Since the rhythm has to be treated a careful but firm attitude is requisite Both quinidine and Pronestyl are effective While there is a trend toward the latter its only established advantage is with parenteral administration Digitalis is generally considered to be contraindicated although this injunction may not necessarily be absolute

Ventricular Fibrillation Ventricular fibrillation is almost always an agonal disturbance which provides very little time for therapy Daring measures are therefore indicated Unless the rhythm develops in a hospital, electrical defibrillation is out of the question Elsewhere, intravenous injection of Pronestyl by vein or even into the heart is the only possible approach

Heart Block Heart block is considered under idioventricular rhythms because therapeutic problems which develop in this condition usually relate to some form of idioventricular difficulty

As previously stated auriculoventricular dissociation per se does not embarrass cardiac function Thus 3 1 and 2 1 block and complete auriculoventricular dissociation are not indications for therapy unless there is clinical evidence that the slow ventricular rate is a source of trouble The fact that the heart is beating

treated with quinidine or Pronestyl While it is a fact that ventricular premature contractions and even ventricular tachycardia due to digitalis can be suppressed by these agents, the justification for their use in these instances is by no means clear On the one hand, ventricular premature contractions are unimportant as any thing but a warning to stop the digitalis, and, on the other hand, the suppression of ventricular tachycardia due to digitalis with quinidine may be more hazardous than the ventricular tachycardia itself More often than not, during the course of digitalis intoxication leading to ventricular tachycardia, heart block develops In these cases successful suppression by quinidine or Pronestyl leads to asystole It is probable that most of the cases of ventricular tachycardia successfully treated with Pronestyl or quinidine were not due to the digitalis the patients were taking but to the heart disease for which they were receiving the digitalis

A method of treating digitalis intoxication with the use of chelating agents to lower blood plasma calcium levels is of considerable interest and may prove to be the most valuable tool we have for this type of poisoning The literature should be watched for developments along this line, but it can already be said that some early reports make this appear to be the most promising therapy for digitalis in toxication thus far

PHARMACOLOGIC BASIS OF THE THERAPY OF DISTURBANCES OF CARDIAC RHYTHM

Disturbances in the cardiac mechanism may be treated either by slowing the rate or substituting a preferable mechanism This may be accomplished by (1) central sedation (2) intensification of vagal tone, (3) depression of cardiac automaticity (4) stimulation of cardiac automaticity, (5) depression of conduction and (6) stimulation of conduction

Central Sedation—Central sedation must be distinguished from any hope to "sedate" cardiac muscle Since a large proportion of cardiac arrhythmias are both paroxysmal and nonthreatening and since many are triggered and sustained by anxieties, sedation may remove the excitant or make tolerable the period of waiting while the disturbance subsides spontaneously Sometimes only sleep is necessary Often the patient permitted to sleep it off is more fortunate than the one subjected to a strenuous therapeutic routine to obliterate the arrhythmia pharmacologically There is further support to the use of a sedative in the form of the barbiturate in animal experiments which indicate direct antiarrhythmic properties in pentobarbital sodium Good clinical judgment is necessary to decide whether the arrhythmia is likely to be so innocuous that the sedative approach is justified

Any of the common sedatives is satisfactory, but a rapid acting drug like pentobarbital seems preferable to a slow acting one such as phenobarbital Sufficient sedative should be used, in general, doses closer to the hypnotic are more likely to be effective than the common sedative dose

Intensification of Vagal Tone—Vagal stimulation is an old and well established approach for the treatment of supraventricular disturbances There are several time honored physical maneuvers Eyeball pressure is sometimes effective but few are able to press strongly enough on the eyes to accomplish anything Carotid sinus pressure has to be applied precisely and therefore is not routinely

effects of etiologic treatment and, should this fail to provide relief, for well considered symptomatic therapy

Thyrotoxicosis Auricular fibrillation and flutter, usually paroxysmal, are seen in thyrotoxicosis, but sometimes the auricular fibrillation persists When the disturbances in rhythm persist or recur frequently, especially when associated with thyrotoxic heart disease, treatment is clearly necessary If the thyroid disease is adequately treated, quinidine is usually effective and the result is permanent

Anesthesia Cardiac arrhythmias occurring during anesthesia tend to excite both surgeons and anesthetists Ventricular as well as auricular arrhythmias may develop The therapeutic situation is comparable to that in thyrotoxicosis in the absence of heart disease, the arrhythmias are rarely threatening and tend to disappear spontaneously, rarely persisting after the anesthetic has been eliminated Unfortunately, it is rarely practical to stop the anesthesia in order to relieve the arrhythmia—although it is sometimes feasible to change the anesthetic—and treatment may become necessary Here, parenteral therapy is indicated and, on this basis, Pronestyl is the drug of choice

Digitalis Arrhythmias are frequently reported as a result of digitalis overdosage Overdigitalization may cause ventricular premature contractions, ventricular tachycardia, ventricular fibrillation, heart block coupling, and occasionally, auricular fibrillation It is my opinion that these are less common than reported and that spontaneous cessation is too often taken to indicate that removal of digitalis or use of potassium abolished the disturbance in rhythm and, hence, to prove a digitalis arrhythmia There is no evidence that one digitalis material is more likely than any other to induce cardiac arrhythmias, it is always a matter of relative dosage

Most of the digitalis materials in common use are excreted relatively slowly—some, like digitoxin, very slowly indeed The prospect of waiting through 24 to 48 hours of intoxication for significant amounts of drug to be eliminated without any treatment tests the sturdiest therapeutist While waiting, it is well to remember that digitalis is given only to patients with heart disease and in this group the incidence of spontaneous arrhythmias is far greater than in the normal population The diagnosis of a digitalis arrhythmia should be made cautiously, for it implies removing the digitalis or at least reducing the intensity of a digitalis effect which the patient may need

Low levels of blood potassium increase the sensitivity of the heart to digitalis, and arrhythmias which develop on this basis can be abolished with potassium Clinical evidence that potassium will help in all cases of digitalis intoxication is not substantial, however Few of the reported successes are supported by laboratory data. The latter are sometimes especially difficult to prove because intracellular potassium deficits are not always reflected in the blood plasma Since potassium itself may be dangerous, especially when given intravenously, it must be given carefully It is my opinion that more often than otherwise the disappearance of cardiac arrhythmias after potassium is due to time rather than kalium In any event, I do not believe that digitalis intoxication warrants the use of potassium unless the disturbance in rhythm threatens cardiac function or hypokalemia is established

Statements are to be found in the literature that digitalis arrhythmias may be

Epinephrine and Isuprel will accelerate the sinus node which, if it becomes more rapid than the ectopic focus, *may then become the pacemaker* Unfortunately, the duration of such an action is not likely to be longer than the short lived action of the drugs themselves Occasionally, however, the abnormal focus *may not reappear when drug effects disappear* Should persistent sinus stimulation be the only way to maintain the sinus as pacemaker, this may be even more undesirable than the arrhythmia itself, since the rate at which sinus control can be maintained is greater than that of the arrhythmia It is of interest that close examination of some of the case records of cardiac arrhythmias abolished by mephentermine indicates that this is precisely what has happened The relative infrequency of a simple sinus bradycardia as a source of cardiac embarrassment accounts for the fact that sinus stimulation per se is not often required or even desirable On the other hand excessive sinus acceleration may be distinctly undesirable in heart disease

More frequently, stimulation of cardiac automaticity is used to accelerate the *ventricular pacemaker in heart block The site of action of epinephrine* and Isuprel in the ventricle is not clear, but both produce the desired effect In the Adams Stokes syndrome due to ventricular asystole or fibrillation, Isuprel prevents or terminates the episode Epinephrine induces other effects which may be undesirable chief among these is ventricular fibrillation There is some dispute whether this does not also apply to Isuprel but most cardiologists seem to think that there is a reduced liability of inducing ventricular fibrillation Isuprel also has no pressor action For these reasons and also because it can be given sublingually, Isuprel is the drug of choice It has virtually replaced all other sympathomimetic amines in the Adams Stokes syndrome

The use of digitalis to stimulate cardiac automaticity requires explanation, largely because its possibilities are rarely explored It may provide an answer in instances in which Isuprel is not successful and other sympathomimetic amines are undesirable The action of digitalis on the myocardial tissues is to increase *rhythmicity In the presence of an idioventricular bradycardia* its effect is to accelerate the ventricular pacemaker or to increase the heart rate through the development of extra ventricular contractions The dose of digitalis necessary to produce such an *effect is in the range of the minor toxic dose*, but done carefully it can be achieved without distress The use of digitalis when the Adams Stokes episodes are due to ventricular fibrillation or tachycardia is another matter Here the contraindication is definite *Before using digitalis for* the Adams Stokes syndrome, it is important to establish precisely the basis of the syncopal episode

Quinidine and Pronestyl are dangerous in heart block *Barium chloride* has long been considered too toxic The usefulness of sodium lactate has yet to be fully explored

Stimulation of Conduction—Stimulation of conduction may be useful in incomplete or functional heart block In marked bradycardia stimulation of conduction may reduce a state of 3 1 to 2 1 block—50 per cent acceleration of ventricular rate While there is no clear evidence for it this is presumed to be one of the actions of the sympathomimetic amines useful in heart block Epinephrine

successful In some instances, holding the breath as long as possible will induc enough vagal tone to slow an auricular tachycardia The results tend to be short lived, but little is lost by trying In this connection it is interesting to note that Demerol (meperidine) has a vagolytic action its use for pain during a cardiac arrhythmia may therefore be followed by acceleration rather than by any beneficial slowing action as is sometimes seen after morphine

More recently pressor agents such as phenylephrine (Neo-Synephrine) and mephentermine (Wyamine) have been used to bring about slowing through intense stimulation of the depressor reflex This device has serious intrinsic hazards and therefore has not been widely practiced

EMESIS —When emesis is associated with sufficient vagal tone, it is sometimes effective in supraventricular disturbances Emesis is essential to the development of sufficient vagal tone, the use of small doses of emetics will fail On the other hand, apomorphine vomiting may be so intense as to be dangerous to a patient with heart disease Consequently, syrup of ipecac is the emetic more commonly used for this purpose It might be added that this disagreeable, although often effective, approach to the therapy of some cardiac arrhythmias is little used today

DIGITALIS —Digitalis exerts a useful effect by lowering the threshold of excitability of the sinus node to vagal stimulation The results are the same as increasing vagal tone It has already been mentioned in the section on sinus tachycardia that where eyeball pressure or emesis fail, digitalization, by sensitizing the sinus node to vagal tone may lead to success when the maneuver is repeated The digitalis material of choice in this instance is a rapidly acting form since speed of onset rather than persistence of action is needed

CHOLINERGIC DRUGS —Vagomimetic drugs, like Mecholyl, have been used in the treatment of supraventricular tachycardias Although their effect is perhaps the most consistent of any which intensify vagal tone, the stimulation of the parasympathetic nervous system is diffuse and, consequently, is associated with widespread disagreeable symptoms Distress closely simulating anginal attacks has been described Patients with a history of allergic reaction are bad subjects, attacks of bronchial asthma may be precipitated These considerations have led to the virtual abandonment of cholinergic drugs in cardiac arrhythmias

Depression of Cardiac Automaticity —Unfortunately, there is no drug with such highly developed specificity of action that it depresses only specific sites of cardiac automaticity Quinidine and Pronestyl are general cardiac depressants, depressing not only automaticity, but also conductivity and cardiac muscle function They do not improve cardiac dynamics by any direct action It is axiomatic, herefore that unless suppression of the arrhythmia is really necessary, these drugs re not really beneficial and may even be harmful Quinidine and Pronestyl may e useful in cases in which they depress an abnormal focus of excitement in doses hich do not significantly depress other cardiac functions when the rhythm they ppress is a source of embarrassment and when the pacemaker they permit to ntrol the heart is a superior substitute

Stimulation of Cardiac Automaticity —Stimulation of cardiac automaticity vides two types of therapeutic action in cardiac arrhythmias stimulation of the mal pacemaker and stimulation of an abnormal pacemaker

VENTRICULAR ARRHYTHMIAS —In general, digitalis materials are contraind cated in idioventricular rhythms other than the special instance of heart blo discussed above More recently the possibility of their use in ventricular arrhyt mias has been reopened but the question is not yet settled

HEART BLOCK —When digitalis is used deliberately to produce persistent bloc longer acting digitalis materials such as digitoxin are indicated for maintenanc When digitalis is used to *increase myocardial rhythmicity in heart block, continu* action is also desired Digitoxin is therefore, the drug of choice

Quinidine —Quinidine is a universal cardiac depressant The safe use of s ic an agent lies in the possibility *that it can depress an undesirable focus of cardi* activity or make it slower so as to permit another more desirable focus to becom the cardiac pacemaker Unlike digitalis, it does not improve myocardial functior Relatively large doses are required for a high order of success When small dose are used to avoid the possibility of toxicity, therapeutic failure is common A *effective regimen must be carefully followed to control the extent of myocardi* depression The electrocardiogram is invaluable for this purpose

There is a tendency for cardiac arrhythmias to reappear after the apparentl successful use of quinidine

In defense of quinidine, it may be said that it is effective against all types o arrhythmias and, therefore may be used when a precise identification cannot be made Second, when it is used in treating arrhythmias due to some form of in toxication or to a cause which can be eliminated, the results are likely to persis *after the drug is removed Finally, as discussed above, some of the accidents* fol lowing the use of quinidine are inherent in the cardiac rhythm and not in the drug and would occur were other drugs successfully used to abolish the abnormality

When quinidine is used in heart block, there is the possibility of disaster, for suppression of the abnormal pacemaker may result in cardiac standstill The use of quinidine to produce gradual *ventricular slowing while following the effects* with the electrocardiograph is the best insurance

Quinidine is slowly absorbed and approximately 2 to 3 hours elapse after an *oral dose before full effects develop* To maintain effects dosage is administered every 3 or 4 hours or if longer intervals are desired the doses must be larger The proper dosage schedule must be explored in each case for so called average *doses* tend to be too small The dose which produces a therapeutic effect without toxic action is the proper one Dosage regimens are altered either by increasing or de *creasing dosage intervals or by* altering individual doses depending on which is more convenient When relatively large doses or short intervals between them are used these should not be adjusted until an electrocardiogram insures *against* ex cessive depressant actions on the myocardium

Quinine is feebler in its cardiac action than quinidine and cannot be substi *tuted for it when any appreciable effect is desired*

PREPARATIONS —There is no difference between the salts of quinidine when oral dosage is contemplated Intravenous use of *soluble quinidine salts is not* con sidered acceptable This view requires reconsideration since the accidents reported about 25 years ago on which the injunction is based were probably due to im

can be used for this purpose, but the longer-acting sympathomimetic amines are preferable Isuprel is the drug of choice

Depression of Conduction—Depression of conduction is a pharmacologic aim in auricular fibrillation because the supraventricular discharges are both rapid and of varying intensity and it is undesirable to have the ventricle respond to all of the impulses Depression of auriculoventricular conduction provides a filterlike action, preventing the feebler impulses from reaching the ventricle As depression is intensified, the ventricular rate is slowed, while the ventricular contractions stimulated only by the stronger supraventricular impulses are both stronger and of more nearly equal intensity Digitalis is the only drug that produces such an effect Unfortunately, this action does not produce the same effects when digitalis is used in a normal cardiac mechanism or in sinus tachycardia Here, progressively larger doses of digitalis produce first partial and then complete block

By perpetuating the state of complete heart block in patients with Adams-Stokes episodes, digitalis may prevent recurrences of attacks of syncope which develop only during the transition from supra to idioventricular pacemakers in intermittent heart block

In all of these instances maintained drug action is desired Digitoxin is, therefore the drug of choice

THE SEVERAL DRUGS

Digitalis Materials—The reader is referred to page 402 for discussions of the several digitalis materials No general statement concerning their choice can be made because in each case it depends on the particular disturbance in rhythm for which treatment is contemplated The choice of digitalis materials is considered here, therefore, only in relation to their use in cardiac arrhythmias and especially in relation to their speed of action

Cardiac Failure—Cardiac failure may induce tachycardia and disturbances of the rhythmic mechanism (1) through accelerator mechanisms, mainly mediated through the sympathetic nervous system, (2) through physical distention due to abnormal chamber pressure, and (3) through hypoxia To the extent that digitalis alleviates failure in these cases it may provide relief for arrhythmia as well Digitalis is indicated in heart failure, and, therefore, this capacity of digitalis to restore a normal mechanism is usually explored as a consequence of the treatment of the heart failure

Vagal Tone—The use of digitalis to increase vagal tone in treating supraventricular arrhythmias is discussed on page 415 The more rapidly acting materials are more desirable, but acetyl strophanthidin, the most rapidly acting, is not easily obtained, and therefore ouabain, which is slower, is usually the best choice

Auricular Flutter—The more rapidly acting digitalis materials such as ouabain should be chosen for the treatment of auricular flutter

Auricular Fibrillation—In treating persistent auricular fibrillation, a long-continued effect is wanted Long-acting digitalis materials such as digitoxin are most fitting, although a more rapidly acting material may be used to produce the first effects when there is need for prompt action

There seems to be no danger in its use in the Adams Stokes syndrome of episodes of ventricular fibrillation or tachycardia, whereas this is a real hazard when some of the other sympathomimetic amines especially epinephrine, are used

Ephedrine and Other Sympathomimetic Amines—Ephedrine and other sympathomimetic amines which are effective orally have been largely replaced by Isuprel in the treatment of heart block Mephentermine (Wyamine), methoxamine (Vasoxyl) and phenylephrine (Neo-Synephrine) have been reported on favorably but there is still considerable question regarding their general utility as well as their safe use in super and idioventricular tachycardias

Potassium—Laboratory evidence indicates that digitalis induced cardiac arrhythmias are sometimes associated with a decrease in blood potassium levels and that the administration of potassium, parenterally or orally, may suppress or prevent such arrhythmias It has been assumed that this applies to similar situations in man and clinical reports support this assumption The suggestion has also been made that parenteral use of potassium may be followed by alleviation of cardiac arrhythmias not associated with the use of digitalis and that the incidence of assistance in these cases approximates the incidence of assistance in patients given digitalis This has not been corroborated and in general the indiscriminate use of potassium has not been successful The present position of potassium in therapy of cardiac arrhythmias—whether due to digitalis or not—is not clear although it appears that there are instances in which it is useful

The best routine for its use is not established Since intravenous injection of potassium is attended by some risk its indications should be determined before that route is used It might be well to give the drug orally until its need is established and the risk of intravenous administration justified

Atropine and Other Vagolytic Agents—Atropine accelerates the sinus rate and in this way may accelerate a slow sinus and assist it in taking control of the heart This action of atropine and other vagolytic agents is more persistent than that of any of the sympathomimetic agents and would seem to be advantageous However, when doses which effectively block vagal tone in the heart are used diffuse effects on salivation and vision, often persisting even longer than the cardiac effects, make the drugs undesirable Reports of their use in preventing attacks of tachycardia in the Wolff Parkinson White syndrome are suspect as is also the prophylactic action against ventricular tachycardia in acute myocardial infarction

Sodium Lactate—Recently evidence has been presented that since lactate appears to increase the rhythmicity of both the sinus node and the ventricle molar sodium lactate may be used in the treatment of patients with slow heart rates Adams Stokes syndrome, and episodes of cardiac arrest Although the initial reports are encouraging and in addition the agent itself seems unlikely to cause any adverse reactions since the precise indications and probable situations of effectiveness have not yet been established it seems appropriate at this time to advise not using the drug in preference to one that is better established but to watch carefully developments in the literature

Chelating Agents—Because of the reciprocal relationship between the intensity of the digitalis effect and the blood calcium level lowering of the blood calcium

ing that Pronestyl can be used intravenously with greater safety than quini
Test doses of quinidine are not likely to reveal any information which would r
subsequent use of the drug safer

Intramuscular preparations of quinidine are available, but they are not
sorbed more rapidly than from the gastrointestinal tract and, therefore, should
considered only for patients who cannot take the drug orally

There is a suggestion in the recent literature that quinidine gluconate indu
quinidine effects which are longer lasting than those induced by the sulfate
quinidine There is no explanation why the gluconate per se should induce pr
longed effects the report in question indicates that the prolonged effects describe
were due to the use of a so-called long acting form of tablet There is also th
recent Report to the Council on Drugs of the American Medical Association
stating that such extended action preparations are too irregular to be relied upon
in critical situations This admonition may apply with more force to some situa
tions with arrhythmia than others

Procaine Amide —There is little evidence to support a contention that Pro
nestyl (procaine amide) is safer or more effective than quinidine Early experiences
with Pronestyl dealt largely with patients who developed arrhythmia as a result of
anesthesia rather than from heart disease The results were excellent and the acci
dents few The drug was used against a background of experience and, in these
hands the initial intravenous experience was a good one What the results would
have been in less experienced hands or in patients whose arrhythmias developed
primarily as a consequence of serious heart disease can only be conjectured With
widespread use in patients with serious heart disease, accidents have certainly been
reported after Pronestyl

Pronestyl continues to be used intravenously because the accidents occurring
after its use have been more carefully analyzed than those occurring after the in
travenous use of quinidine Current usage, however defends the former and con
demns the latter, and until the issue is clarified—especially since there is no decided
advantage in quinidine—Pronestyl will be the drug of choice for intravenous use
The intramuscular preparation of Pronestyl has a clear advantage over the intra
muscular preparation of quinidine because effects develop more rapidly Orally,
there is probably no basis for a choice

All dangers inherent in the treatment of cardiac arrhythmias which apply to
quinidine apply equally to Pronestyl

Epinephrine —Epinephrine has been employed principally in treating heart
block Its use to accelerate a slow or normal sinus in order to replace an aberrant
pacemaker with a normal one has limitations because of its brief action and the
danger of ventricular fibrillation In all instances of cardiac arrhythmias, it has
been largely displaced by Isuprel

Isoproterenol —Isoproterenol (Isuprel) stimulates automaticity in specialized
cardiac tissue and perhaps also in the muscle mass itself The precise localization
of all its effects have not been charted, but the influence on rate together with an
absence of pressor action make it the drug of choice in heart block It may enhance
A V conduction Since it can be taken sublingually and produces lasting effects
has supplanted other sympathomimetic drugs for this purpose

There seems to be no danger in its use in the Adams Stokes syndrome of episodes of ventricular fibrillation or tachycardia, whereas this is a real hazard when some of the other sympathomimetic amines especially epinephrine, are used

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The best routine for its use is not established Since intravenous injection

Atropine and Other Vagolytic Agents—Atropine accelerates the sinus rate and in this way may accelerate a slow sinus and assist it in taking control of the heart This action of atropine and other vagolytic agents is more persistent than that of any of the sympathomimetic agents and would seem to be advantageous However, when doses which effectively block vagal tone in the heart are used diffuse effects on salivation and vision, often persisting even longer than the cardiac effects make the drugs undesirable Reports of their use in preventing attacks of tachycardia in the Wolff Parkinson White syndrome are suspect as is also the prophylactic action against ventricular tachycardia in acute myocardial infarction

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Chelating Agents—Because of the reciprocal relationship between the intensity of the digitalis effect and the blood calcium level lowering of the blood calcium

through the action of a chelating agent will reduce the toxic effects of digitalis In attempting to treat digitalis intoxication in this way it is well to remember, however, that in this case the chelating agent is not the *calcium* edathamil, which will not chelate calcium, but the *sodium* salt, which will Large doses of the latter, of course will lower blood calcium sufficiently to induce hypocalcemic tetany and even death and, used over a long period of time in small doses, will cause demineralization of the bones

Others—Recently, and this may be taken as evidence of the current wide search for antiarrhythmic agents superior to those in common use and described above, reports of antiarrhythmic properties of a wide variety of unrelated drugs have appeared in the literature It has been shown in our laboratory that pentobarbital has this property, by others that this is true of chloroquine and other antimalarial agents, hydroxyzine, reserpine, and other ataractics, etc Clinical trials with these drugs along these lines have not been carried out sufficiently, however, for any substantial opinion of their practical value in the treatment of cardiac arrhythmias

Barium Chloride —Barium chloride is too toxic to use

Aconite—Aconite is an archaic drug

A DESIGN FOR THE USE OF DRUGS IN CARDIAC ARRHYTHMIAS

The indications for treatment of cardiac arrhythmias are variable There are arrhythmias (1) which are not a threat to cardiac function or which are likely to cease spontaneously before they threaten function, (2) which are not a threat to function but which impinge on consciousness sufficiently to require therapy, (3) which embarrass cardiac function but which do not urgently require treatment, and (4) which constitute an immediate threat to life and require prompt and even heroic attention Depending upon the category into which the arrhythmia falls the symptom can be left untreated the patient can be given well-considered, well planned, and carefully tested treatment, the patient must be promptly subjected to treatment most likely to ameliorate the situation in the shortest time The cause of the arrhythmia and identification of its nature play important roles in determining the best design of treatment Other features such as the existence of heart disease its nature and severity, the presence of heart failure, preceding or as a result of the arrhythmia, the patient's general condition, the presence of noncardiac diseases and the state of shock, all modify the course to be taken and the choice of drugs

Effectiveness and safety in treating cardiac arrhythmias also rest on the knowledge of when to treat as well as how to treat The danger of embolization in auricular fibrillation is inherent in the initial decision to restore a normal rhythm An inconsequential ectopic rhythm replaced by ventricular fibrillation may result in disaster, while the replacement of a sinus bradycardia by a sinus tachycardia may aggravate matters for the patient

A large number of cardiac arrhythmias are short-lived and inconsequential while at the same time they are difficult to suppress The best therapy is to have the patient accept these arrhythmias He may be assisted by nonspecific sedative or hypnotic therapy Often, the patients sleep off their palpitations

There seems to be no danger in its use in the Adams Stokes syndrome of episodes of ventricular fibrillation or tachycardia, whereas this is a real hazard when some of the other sympathomimetic amines, especially epinephrine are used

Ephedrine and Other Sympathomimetic Amines—Ephedrine and other sympathomimetic amines which are effective orally have been largely replaced by Isuprel in the treatment of heart block Mephentermine (Wyamine) methoxamine (Vasoxyl and phenylephrine (Neo Synephrine) have been reported on favorably but there is still considerable question regarding their general utility as well as their safe use in super and idioventricular tachycardias

Potassium—Laboratory evidence indicates that digitalis induced cardiac arrhythmias are sometimes associated with a decrease in blood potassium levels and that the administration of potassium parenterally or orally, may suppress or prevent such arrhythmias It has been assumed that this applies to similar situations in man and clinical reports support this assumption The suggestion has also been made that parenteral use of potassium may be followed by alleviation of cardiac arrhythmias not associated with the use of digitalis and that the incidence of assistance in these cases approximates the incidence of assistance in patients given digitalis This has not been corroborated and in general the indiscriminate use of potassium has not been successful The present position of potassium in therapy of cardiac arrhythmias—whether due to digitalis or not—is not clear although it appears that there are instances in which it is useful

The best routine for its use is not established Since intravenous injection of potassium is attended by some risk its indications should be determined before that route is used It might be well to give the drug orally until its need is established and the risk of intravenous administration justified

Atropine and Other Vagolytic Agents.—Atropine accelerates the sinus rate and in this way may accelerate a slow sinus and assist it in taking control of the heart This action of atropine and other vagolytic agents is more persistent than that of any of the sympathomimetic agents and would seem to be advantageous However when doses which effectively block vagal tone in the heart are used diffuse effects on salivation and vision, often persisting even longer than the cardiac effects make the drugs undesirable Reports of their use in preventing attacks of tachycardia in the Wolff Parkinson White syndrome are suspect as is also the prophylactic action against ventricular tachycardia in acute myocardial infarction

Sodium Lactate—Recently evidence has been presented that since lactate appears to increase the rhythmicity of both the sinus node and the ventricle molar sodium lactate may be used in the treatment of patients with slow heart rates Adams Stokes syndrome, and episodes of cardiac arrest Although the initial reports are encouraging and in addition the agent itself seems unlikely to cause any adverse reactions since the precise indications and probable situations of effectiveness have not yet been established, it seems appropriate at this time to advise not using the drug in preference to one that is better established but to watch carefully developments in the literature

Chelating Agents—Because of the reciprocal relationship between the intensity of the digitalis effect and the blood calcium level lowering of the blood calcium

through the action of a chelating agent will reduce the toxic effects of digitalis In attempting to treat digitalis intoxication in this way it is well to remember, however, that in this case the chelating agent is not the *calcium* edathamil, which will not chelate calcium, but the *sodium* salt which will Large doses of the latter, of course, will lower blood calcium sufficiently to induce hypocalcemic tetany and even death and used over a long period of time in small doses, will cause demineralization of the bones

Others.—Recently, and this may be taken as evidence of the current wide search for antiarrhythmic agents superior to those in common use and described above, reports of antiarrhythmic properties of a wide variety of unrelated drugs have appeared in the literature It has been shown in our laboratory that pentobarbital has this property, by others that this is true of chloroquine and other antimalarial agents, hydroxyzine, reserpine, and other ataractics, etc Clinical trials with these drugs along these lines have not been carried out sufficiently, however, for any substantial opinion of their practical value in the treatment of cardiac arrhythmias

Barium Chloride.—Barium chloride is too toxic to use

Aconite.—Aconite is an archaic drug

A DESIGN FOR THE USE OF DRUGS IN CARDIAC ARRHYTHMIAS

The indications for treatment of cardiac arrhythmias are variable There are arrhythmias (1) which are not a threat to cardiac function or which are likely to cease spontaneously before they threaten function, (2) which are not a threat to function but which impinge on consciousness sufficiently to require therapy, (3) which embarrass cardiac function but which do not urgently require treatment, and (4) which constitute an immediate threat to life and require prompt and even heroic attention Depending upon the category into which the arrhythmia falls the symptom can be left untreated the patient can be given well considered, well planned, and carefully tested treatment the patient must be promptly subjected to treatment most likely to ameliorate the situation in the shortest time The cause of the arrhythmia and identification of its nature play important roles in determining the best design of treatment Other features such as the existence of heart disease its nature and severity, the presence of heart failure, preceding or as a result of the arrhythmia, the patient's general condition, the presence of non cardiac diseases and the state of shock, all modify the course to be taken and the choice of drugs

Effectiveness and safety in treating cardiac arrhythmias also rest on the knowledge of when to treat as well as how to treat The danger of embolization in auricular fibrillation is inherent in the initial decision to restore a normal rhythm An inconsequential ectopic rhythm replaced by ventricular fibrillation may result in disaster, while the replacement of a sinus bradycardia by a sinus tachycardia may aggravate matters for the patient

A large number of cardiac arrhythmias are short lived and inconsequential, while at the same time they are difficult to suppress The best therapy is to have the patient accept these arrhythmias He may be assisted by nonspecific sedative or hypnotic therapy Often, the patients sleep off their palpitations

In many cases, external causes such as intoxications can be found Sometimes but less often than patients believe, excessive use of coffee or tobacco causes arrhythmias In any event, all external causes *should be eliminated* *Often, however*, these include anxiety charged situations, family difficulties, and problems and irritants in work which, even when identified are difficult to remove

For paroxysmal arrhythmias, preventive therapy is more desirable than treatment of the attack The setting in which attacks develop may be an important factor Treatment at home is often more difficult than treatment in the hospital *Success will be more frequent when this difference is accepted and when equal, if* not larger, dosage of drugs are used in the prophylaxis of attacks than in treating them Because this is so, prophylactic therapy is warranted only when the attacks are severe

Where treatment is indicated, the decision has to be made whether to obliterate the abnormal rhythm or to slow the rate since the former requires not only removal of the ectopic focus but provisions for a new and effective pacemaker If there is permanent heart block, it is clear that an idioventricular rhythm cannot be replaced by a normal rhythm

It is safer to use quinidine and Pronestyl to depress than to obliterate ectopic foci It is good practice in all cases, especially since the decrease of a rapid rate is in itself a therapeutically significant accomplishment Although ventricular tachycardia is a serious arrhythmia, the ventricle responds with an organized contraction to the ectopic focus, slowing is therefore useful Only in the completely disorganized and ineffectual fibrillation of the ventricle is the termination of the rhythm and its replacement by another mechanism for *ventricular stimulation an* absolute necessity Here is the indication for heroic measures

Dosage —There are no absolute dosages in the treatment of cardiac arrhythmias The amount of drug necessary varies widely with the disturbance of rhythm and the heart disease present Biologic effects must be the guides to dosage and dosage regimens In the more serious situations in which relatively large doses of depressant drugs such as quinidine or Pronestyl are used, it is wise to follow with the electrocardiogram to determine whether or not serious myocardial depression is developing

RATIONAL BASIS OF NEW DRUGS FOR THE RELIEF OF CARDIAC ARRHYTHMIAS

The existing need is for drugs with highly selective depressant actions on cardiac function Quinidine and Pronestyl are effective in all cardiac arrhythmias and may be used therefore in cases where there is no precise diagnosis, but their universal action limits utility Drugs with a selective action on pacemaker *tissue*, conducting tissue, and auricular or ventricular muscle are much to be desired

As matters stand, such a drug is not available Statements that a new drug has such actions must be examined carefully When Pronestyl *was introduced* it was stated that it was superior to quinidine in its ventricular effects but inferior in auricular effects Further experience showed this claim to be unsubstantial and also that the greater safety claimed for Pronestyl *was equally meretricious*

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CLINICAL APPLICATIONS

Coronary Occlusion —The *pain of the myocardial infarction is characteristically severe,* resistant to the coronary dilators, and difficult to relieve even with morphine

When coronary dilators alleviate severe precordial pain, this militates against a diagnosis of coronary infarction Occasionally, however, the pain is relieved in cases in which electrocardiograms and post mortem examination prove the existence of infarction In such instances, it may be assumed that the dilator action was central to the completely occluded portion of the coronary artery, perhaps in constricted segments of the coronary arteries adjacent to the occlusion which on dilatation permitted the flow of blood to some hypoxic areas of myocardium This assumption provides the only rational basis for the continued use of coronary dilators in myocardial infarction to improve circulation to areas adjacent to the infarction to promote the healing and subsequent revascularization of the infarcted area It was for this purpose that aminophylline and others of the xanthine series were recommended in the treatment of coronary infarction The evidence for this kind of therapy was analyzed by Gold and his associates some years ago both in animals, in which the influence of the drugs on the size of the infarct was examined and in man, in whom the effects on the coronary pain were evaluated In each case aminophylline was found wanting Since then, the use of drugs for this purpose has been virtually abandoned

In summary, it might be stated that in the therapy of the myocardial infarction the presently available coronary dilators provide little for the relief of its pain while there is no good evidence that they assist in the growth of new blood vessels to the infarcted area of the heart or in any other way accelerate healing Their only utility lies in the dilatation of vessels in spasm as a reaction to occlusion

Anginal Syndrome —*For purposes* of exploring the physiologic and pharmacologic basis for the use of agents to relieve the pain, this syndrome may be divided into six categories (1) hypoxia of the myocardium due to coronary artery spasm (2) hypoxia due to coronary insufficiency, (3) hypoxia due to low diastolic pressure (4) hypoxia due to other cardiodynamic disturbances, (5) hypoxia due to respiratory disturbances and (6) hypoxia due to extracardiac disturbances

Coronary Artery Spasm —Regardless of the merits of the arguments presented concerning the mechanism of pain and its relief in the anginal syndrome the fact remains that the nitrites are pre eminent in the relief of its pain

In this situation proper dosage with nitrite rarely *fails to provide relief* As a matter of fact so consistent is this action of the nitrites that it is used for diagnostic purposes failure of the nitrites to relieve the pain casts doubt on the diagnosis of spasm of the coronary arteries

Drugs such as khellin and xanthines, are not effective in relief of acute pain They will be considered in more detail below but it is clear even in the reports of the most enthusiastic they are neither as potent nor as consistent in providing relief as are the nitrites

The use of coronary artery dilators for the prevention of anginal attacks is another matter Here there is considerable dispute regarding the value *of* any *of* them, even the nitrites In many patients, the incidence of attacks of anginal pain

The drugs presently available may be given orally therefore, no particular advantages are manifest in a new drug unless its oral action is more quickly developed The dangers of intravenous therapy with quinidine require reassessment before still another quinidine like drug is credited with being safer by that route

CHOICE OF A CORONARY ARTERY DILATOR

INTRODUCTION

The coronary artery dilators are so named because of presumptions that the mechanism of the pain of the anginal syndrome is insufficient coronary blood flow and that agents which relieve the pain must, therefore, dilate the coronary arteries to accomplish this

The first presumption is that this pain is the consequence of hypoxia of the actively beating myocardium In support of this contention is the fact that similar pain develops in its severest form in the unquestioned hypoxia of myocardial infarction Further support is found in a model If the blood supply to the arm is cut off with a blood pressure cuff and the hand contracted regularly, unendurable pain develops The pain disappears as soon as the circulation to the arm is restored This corresponds to anginal pain induced by cardiac contractions during hypoxia and relief of the pain by the nitrites, which are accepted as coronary artery dilators

The second presumption that drugs which relieve this pain do so by relieving constriction of the coronary artery is based on the observation that the nitrites induce relaxation of all smooth muscle including that of the arterial system The inference that there is specialized coronary dilatation is based on the observation that anginal pain may be relieved by nitrites without producing generalized hypotension and since anginal pain is presumed to be due to coronary spasm, anything which relieves the pain must do so by relieving the spasm

This then, is an example of circular reasoning in which the proof of specific coronary artery dilatation by nitrites rests on the presumption that the pain is due to constriction of the coronary arteries, while the weight of the latter presumption rests on the fact that the pain is relieved by nitrites While both presumptions are very likely true neither is proved for there are no direct observations of a spasm of a coronary artery during an anginal attack or its relaxation by a nitrite Electrocardiographic changes do not provide more definite proof Direct observations on coronary flow before and during anginal pain and before and after its relief by nitrites are now in progress and should provide a proper conclusion for this semantic concern over the reputed mechanism of anginal pain Nevertheless it is a generally accepted and useful hypothesis and it is also probably a fact that anginal pain is due to a state of hypoxia in an area of actively contracting cardiac muscle resulting from spasm of a branch of the coronary arteries and that the spasm and the pain it causes are relieved by drugs which relatively specifically relieve the spasm of the coronary arteries It is to be emphasized that this specificity of action is essential in any drug used for coronary spasm for obvious reasons diffuse arterial dilatation is highly undesirable

through the use of diuretics is discussed in the appropriate section (page 87) In so far as it represents hypoxia due to transudation of fluid into the pulmonary bed on assuming the recumbent position, this can be relieved and prevented by the judicious use of diuretics and digitalis or more simply, if not medicinally, by propping the patient up in bed *Vasodilating drugs are of little value in this pain*

NONCARDIAC DISEASES —There is a variety of extracardiac diseases—particularly anemias and hypothyroidism—in which there may be relative myocardial hypoxia The combination with a degree of coronary sclerosis is even more likely to result in anginal pain Since here there is no spasm of the coronary artery, the coronary dilators cannot be expected to be useful, in fact they might make matters worse On the other hand, relief of the extracardiac cause may provide excellent relief of the pain

PHARMACOLOGIC BASIS OF THERAPY

Pharmacodynamic Actions —The pharmacologic action needed for myocardial hypoxia is increase of coronary blood flow This may be accomplished by an increase in blood pressure as a result of increased cardiac output or an increase in the caliber of the coronary arteries

Increase in cardiac output increases the work of the heart While such an action might be applicable to anginal pain due to noncardiac conditions, in heart disease this action is not desirable

Increased coronary flow through specific dilatation of the coronary artery is theoretically ideal Such an effect does not increase the work of the heart It restores the myocardium to a more nearly normal state of nutrition and perhaps reduces the insult to it

The drugs which effectively dilate the coronary arteries are relatively nonspecific The nitrites, which may be used as the example of the effective coronary dilator relax all smooth muscle This diffuse action results in relaxation of smooth muscle of bile ducts, gastrointestinal tract, bronchial tree, ureters, and arterioles In general, the arterioles are more sensitive to this action than the remaining structures with smooth muscle, so that depression in blood pressure usually develops before any important action on smooth muscle in other systems This relative selectivity confines the utility of the nitrites to the vascular system

The selectivity of areas of arterial dilatation is another matter Evidence for a highly specific action on the coronary arteries is not conclusive Though there are experiments in which direct measurements indicate both dilatation and increase in blood flow in the coronary arteries following nitrites and other vasodilating agents there is no evidence that dilatation does not also occur elsewhere

Only in the patient with anginal syndrome is there a pharmacologic effect after the nitrites without diffuse action resulting in hypotension It may be that the drugs useful in this condition exert a specific effect only in the presence of abnormal arterial sensitivity and that this special state is spasm of the coronary artery and therefore, that such small doses can be used for the relief of spasm that they do not induce a systemic effect If this is so it casts considerable doubt on the utility of the same drugs for improving coronary circulation when there is no spasm

relates to anxiety and extraneous forces In so far as these tend to produce tacks, placebo and sedative, rest and relaxation, and even reassurance all ten prevent them Since all or most of these are concomitants of the doctor's tr ment with nitrite or with any other so-called coronary dilator, there is great di culty in determining their action in preventing anginal attacks As matters sta the picture is utterly confused and the usefulness of drugs for this purpose requi careful re-evaluation

CORONARY INSUFFICIENCY —In coronary insufficiency, myocardial hypoxia presumed to be due to narrowed lumina of coronary arteries which, though abl to conduct sufficient blood for basal requirements, are functionally insufficient wher the heart muscle requires more Pain produced by this mechanism is not due to coronary spasm Coronary artery dilators now available have little effect on scle rotic vessels, they are effective dilators of soft and reactive arteries Inasmuch as coronary insufficiency is fundamentally due to arteriosclerotic changes, the drugs now available can be expected to improve coronary circulation very little As might be anticipated, experience proves that the pain of coronary insufficiency is not relieved by nitrites or other coronary artery dilators Removal of calcifications from coronary arteries by chelation has been tried, but unfortunately for most of us the results have been uniformly negative

LOW DIASTOLIC BLOOD PRESSURE —There may be typical anginal pain in aortic valvular insufficiency Here myocardial hypoxia is the result of very low diastolic blood pressure which fails to force enough blood through the coronary arteries for myocardial needs In this situation, there already is physiologic vaso dilatation, viz, the bottomless blood pressure and the capillary pulsations seen in the nail beds Coronary artery dilation would, therefore, not be useful This is the usual clinical finding, and in patients in whom it is otherwise it is necessary to reconsider the nature of the circulatory defect causing the pain

MISCELLANEOUS CARDIAC DISTURBANCES —Typical anginal pain also occurs in pericarditis, myocarditis, cardiac arrhythmias, and cardiac failure In the inflammatory conditions, the radiation of pain may be classic for angina, but since there is no defect in coronary circulation, neither nitrites nor other dilators provide relief In cardiac arrhythmias, in so far as circulatory deficiency may cause myocardial hypoxia, relief of the rhythmic disturbance may relieve the anginal pain Similarly, when congestive heart failure provides less blood or less oxygen to the myocardium than is needed, there may be pain which is relieved when the cardiac failure is relieved (page 395) Anginal pain increases in incidence as these cardiac difficulties combined with a degree of coronary artery sclerosis together induce enough myocardial hypoxia to cause pain where each alone was insufficient

RESPIRATORY DISTURBANCES —Respiratory insufficiency, uncomplicated by oronary disease, is not commonly associated with typical anginal pain, but, if it s associated with coronary sclerosis there may be anginal pain In this situation, oor oxygenation of blood and reduction in the lumina of the coronary arteries ombine to produce myocardial hypoxia

Anginal pain sometimes develops in these patients only when they assume the umbent position, the *angina decubitus* This form of pain may be presumed to an expression of left sided heart failure and, as such, its genesis

extremely rapid curve of action The other nitrite drugs have appreciably longer curves of action but in all other respects they appear pharmacologically similar They may profitably be considered as a group

ACTIONS —It has long been assumed that the action of these drugs is related to the liberation of the nitrite ion More recently, however, this conception has been questioned and it has been suggested that it is the organic nitrate per se which actually does the job

The action on the coronary arteries is to relax smooth muscle This applies to all smooth muscle arterial, intestinal, biliary, ureteral, and bronchial Action on the coronary arteries is supported by studies in which nitrites have been shown to prevent the typical electrocardiographic effects of the exercise tolerance test in patients with coronary sclerosis

A selective action on the coronary arteries without producing systemic hypo tension may be explained by the presumption that the arterial smooth muscle in spasm is relatively sensitive to the action of the nitrite While nitrites may re lieve anginal pain without other symptoms in the normal person the first per ceptible nitrite action usually is severe headache or other evidence of diffuse action When the coronary arteries are physically occluded by a thrombus the nitrites do not relieve the pain On the other hand these drugs do not relieve the pain of intermittent claudication but here the presence of relatively advanced arterio sclerosis may be the interfering factor

TOLERANCE —The regularity with which tolerance is developed to the nitrites is outstanding This is important in both medicine and industry

In industry tolerance is a valuable attribute of the nitrites its development makes possible continued work with nitrites New workers develop severe head aches but the headaches disappear within a few days This tolerance is short lived however and if the worker fails to be exposed during a brief illness or a long week end his tolerance is likely to vanish To avoid this loss, workers carry some nitrite with them when they leave their work Men often put nitroglycerin in their hat bands The material is volatile and the small amounts of the nitrite in the atmosphere is sufficient to keep them from losing their tolerance

In medicine the same feature of the nitrites stands in the way of prophylaxis If the nitrites are given too frequently during the day or if a long acting compound is used which liberates nitrite slowly into the blood stream the likelihood of toler ance is great However its brief duration means that if a patient develops tolerance through excessive use, a few days of abstinence is sufficient to restore the former efficacy of the drug

DANGERS —Hypotension caused by diffuse nitrite action is usually caused by administration to unsuitable patients or by inappropriate dosage

Methemoglobinemia is a relatively rare occurrence in the nitrite industry It rarely if ever occurs in medicine after therapeutic doses even when taken very frequently It commonly develops after massive single doses taken accidentally e g , the ingestion of the contents of a bottle of pills by an infant

There is the possibility of increase in intraocular pressure due to dilatation of intraocular vessels which may constitute a danger in incipient glaucoma This does not develop after doses only large enough to dilate the coronary artery in

The rate of onset of action of the coronary dilators is an important element in their choice In general the curves of action follow a symmetrical pattern Those drugs whose actions develop rapidly exert effects equally briefly and, conversely those whose actions come on slowly exert the action for a relatively longer period of time

For the relief of an attack of coronary pain, the most rapidly acting drug is the most desirable Most attacks of anginal pain subside promptly on resting When a drug with considerable latency is used, rest may relieve the pain before the pharmacologic effect of the drug develops Only when the speed of action approximates that of amyl nitrite is there no question of a cause and effect relationship between drug and relief of pain From this point of view, none of the drugs available are superior or equal to amyl nitrite and nitroglycerin

Once the pain disappears no further drug action is necessary Were it otherwise pain would return soon after its relief Thus, long acting coronary artery dilators begin to act after the pain is relieved spontaneously and continue to exert their effects long after the need has disappeared

Interest in persistent action stems from a real need for a drug for preventing attacks Several problems are posed by this prophylactic goal if the drugs now available are to be used In addition the nitrites the most useful of the dilators of the coronary artery have a well developed propensity for the induction of tolerance with continued use

Another approach is to provide a continued concentration of vasodilator drug which will not influence blood pressure but will dilate the artery in spasm promptly, hence relieving pain virtually before it develops For this purpose a host of so called slow acting or delayed absorption nitrites have been introduced There is no evidence that it is possible to provide, on a continuing basis the delicate balance between diffuse effect and prophylactic effect on which such a program is postulated

The literature abounds in contradictory statements regarding this possibility Some suggest that we do have effective agents for the continued prophylaxis of anginal pain others are certain of their negative results Many of the studies are obviously poor and do not provide substantial answers to this important problem

Dangers Inherent in Coronary Artery Dilators—The chief danger inherent in the drugs now in use lies in the fact that none is a specific coronary dilator Those which are useful apparently depend on the existence of the special circumstance of spasm The danger is that the therapeutic action will extend to other vascular beds and induce generalized hypotension Beyond this, the dangers of toxicity are due to the properties of particular drugs.

Tolerance—This is an especially pertinent problem, for a high order of tolerance does develop to nitrites This is an important factor in limiting the prophylactic value of nitrites

THE SEVERAL DRUGS

The Nitrites—The nitrites comprise a list of drugs of which amyl nitrite and nitroglycerin are the best known and the most used They are distinguished by an

the patient as in the case of the nitrite taken by inhalation Nitroglycerin is therefore considerably safer for the patient to use in the physician's absence

The effects of nitroglycerin take a bit longer to develop and last a bit longer than those of amyl nitrite It has usefulness as a prophylactic agent in special circumstances *Patients who know they are to be exposed to an emotion charged situation may be effectively primed with a tablet 15 minutes before the exposure* On the other hand, used *regularly through the day to prevent attacks, it is usually ineffective*

There are patients who regularly take 30 or more tablets daily, apparently with undiminished effectiveness In these patients there are the unsettled questions whether they take so many because there is tolerance and the relief is psychologic and whether the agent of relief is the rest they invariably take with the tablet

Sustained release capsules and tablets are now available Every argument against the utility of nitroglycerin for continuous phophylaxis applies here In addition there is the fact that nitroglycerin is destroyed in the liver so that administration by mouth with absorption into the portal circulation is ineffective For this reason therefore orally administered nitroglycerin is useless Yet this *is the means by which the so called sustained release form of nitroglycerin is used* Recent studies have indicated that it is without clinical value To what extent *this applies to other orally administered organic nitrates has not been established*

LONG ACTING NITRITES —

Sodium Nitrite *Although it is almost never used in angina* sodium nitrite is mentioned because it represents the first form of the drug used clinically Since it continues to be used in medicine and industry, its typical nitrite action on blood vessels is still important

Organic Nitrates This comprises a large group of nitrates which exert relatively prolonged nitrite actions Nitroglycerin is really one of the organic nitrates but its rapid curve of action is exceptional The typical curve of action has long been attributed to the rate of liberation of nitrite, the rate of development of action and its duration relating directly to the rate at which this biotransformation occurs Recently the question has been raised whether this occurs at all and whether it is not that each drug acts in its original state The merits of each case are not argued here *for regardless of which turns out to be the fact, it is* important that the fundamental pharmacodynamic action is the same as that of amyl *nitrite in all instances* The curves of action of the members of the group differ little

Since they all have relatively slow curves of action as a group their use as prophylactic agents is their most attractive therapeutic potential and it is for this purpose that their manufacturers promote them

Each of these agents is used hopefully when introduced but with decreasing enthusiasm as the attempt to achieve prophylaxis proves elusive

The drugs belonging to this series and now in use follow erythrityl tetranitrate (Erythrol Tetranitrate) inositol hexanitrate (Tolanate), mannitol hexanitrate (*Maxitate Nitranitol*) *pentaerythritol* tetranitrate (Angicap Nitrotalans Pentrate) triethanolamine trinitrate (aminotrate Metamine) The fact that these drugs are now commonly sold in mixtures which contain ataractics or barbiturates

spasm, hence it is exceedingly rare as a complication of the treatment of the anginal syndrome

Headache, sometimes exceedingly severe, may complicate the use of nitrites This symptom is unnecessary, for in most instances the headache results from excessive doses If headache follows the use of even the smallest common doses, say 0 3 mg of nitroglycerin, before the drug is discarded as useless, still smaller doses should be tried In some cases, doses half that size have been effective

Nitrite syncope is an unpredictable complication and has been reported from as little as 0 25 mg, although it is usually the result of appreciably larger doses It is believed to be due to dilatation of the capillary bed It is aggravated by the orthostatic position and often can be overcome by placing the patient in a horizontal position Statements in the literature indicate that this complication is not rare but this has not been my experience This discrepancy may possibly be attributed to the fact that I always use the smallest effective doses

Rapid Acting Nitrites —Rapid acting nitrites take effect within a fraction of a minute after application

Amyl Nitrite Amyl nitrite is a volatile material which produces its effects more promptly than any other nitrite It is administered by inhalation Its u[illegible] is conspicuous and dramatic Its administration is punctuated by the explo[illegible] noise of the vial breaking and its pervasive, unpleasant odor Everyone abou[illegible] soon aware of it some even suffering headache It is usually limited to instan[illegible] where speed is the prime consideration

It is dispensed in sealed vials covered with fabric which soaks up the l[illegible] and contains the glass fragments of the broken vial The vials contain far [illegible] amyl nitrite than is required for a single dose, it should be withdrawn therefore [illegible] soon as satisfactory effect develops Dosage is difficult to control and, as a [illegible] caution, the patient should be lying down or at least sitting when the d[illegible] administered

Octyl Nitrite Octyl nitrite (Octrite) is another rapid acting agent [illegible] administered by inhalation Dosage is controlled by the patient, and ser[illegible] dosage is possible Although its odor is not as unpleasant as amyl nitr[illegible] no other advantages over the latter It is relatively expensive and is [illegible] used

Nitroglycerin The official name for nitroglycerin, glyceryl trinitra[illegible] parently chosen with little regard for the resistance of the medical [illegible] new names especially to one longer than the traditional name Ther[illegible] hope that the profession will call it glyceryl trinitrate as there is fo[illegible] acetylsalicylic acid rather than aspirin The term nitroglycerin will [illegible] therefore

The pharmacologic effects of nitroglycerin develop almost ins[illegible] lingual application Oral administration is ineffective for reaso[illegible]

Since the dose is minute, the tablets are small and a large num[illegible] ried inconspicuously Although there are advantages in adminis[illegible] quires the cooperation of the patient, whereas even the uncon[illegible] be made to breathe amyl nitrite

Since the dosage form is fixed, it is controlled by the phys[illegible]

the patient as in the case of the nitrite taken by inhalation Nitroglycerin is therefore considerably safer for the patient to use in the physician's absence

The effects of nitroglycerin take a bit longer to develop and last a bit longer than those of amyl nitrite It has usefulness as a prophylactic agent in special circumstances Patients who know they are to be exposed to an emotion charged situation may be effectively primed with a tablet 15 minutes before the exposure On the other hand used regularly through the day to prevent attacks it is usually ineffective

There are patients who regularly take 30 or more tablets daily, apparently with undiminished effectiveness In these patients, there are the unsettled questions whether they take so many because there is tolerance and the relief is psychologic and whether the agent of relief is the rest they invariably take with the tablet

Sustained release capsules and tablets are now available Every argument against the utility of nitroglycerin for continuous phophylaxis applies here In addition there is the fact that nitroglycerin is destroyed in the liver so that administration by mouth with absorption into the portal circulation is ineffective For this reason therefore orally administered nitroglycerin is useless Yet this is the means by which the so called sustained release form of nitroglycerin is used Recent studies have indicated that it is without clinical value To what extent this applies to other orally administered organic nitrates has not been established

LONG ACTING NITRITES —

Sodium Nitrite Although it is almost never used in angina sodium nitrite is mentioned because it represents the first form of the drug used clinically Since it continues to be used in medicine and industry, its typical nitrite action on blood vessels is still important

Organic Nitrates This comprises a large group of nitrates which exert relatively prolonged nitrite actions Nitroglycerin is really one of the organic nitrates but its rapid curve of action is exceptional The typical curve of action has long been attributed to the rate of liberation of nitrite, the rate of development of action and its duration relating directly to the rate at which this biotransformation occurs Recently the question has been raised whether this occurs at all and whether it is not that each drug acts in its original state The merits of each case are not argued here for regardless of which turns out to be the fact it is important that the fundamental pharmacodynamic action is the same as that of amyl nitrite in all instances The curves of action of the members of the group differ little

Since they all have relatively slow curves of action as a group their use as prophylactic agents is their most attractive therapeutic potential and it is for this purpose that their manufacturers promote them

Each of these agents is used hopefully when introduced but with decreasing enthusiasm as the attempt to achieve prophylaxis proves elusive

The drugs belonging to this series and now in use follow erythrityl tetranitrate (Erythrol Tetranitrate), inositol hexanitrate (Tolanate), mannitol hexanitrate (Maxitate Nitranitol) pentaerythritol tetranitrate (Angicap Nitrotalans Peritrate) triethanolamine trinitrate (aminotrate Metamine) The fact that these drugs are now commonly sold in mixtures which contain ataractics or barbiturates

as well as the fact that patients using them are also regularly inst nitroglycerin with them "just in case," shows the uncertain confide ponents really have for their prophylactic utility

SUMMARY—The nitrites are pre eminently useful in the relief attack of anginal pain Here the rapid acting members far outstrip t satisfying the requirements The choice for this purpose depends o venience and ease of controlling dosage and application Usually, ni is the choice On the other hand, where seconds or fractions of minute portant amyl nitrite is superior

The history of failures with so called long acting nitrites is an unbro From our understanding of the action of these drugs, such a quality is no the province of nitrite action and should be sought in some other type o Since they could have no other useful attribute, no so called long acting is the drug of choice in the anginal syndrome

Monamine Oxidase Inhibitors—A rather large group of agents belongi this series, iproniazid (Marsilid) isocarboxazid (Marplan), β phenyl isopro hydrazine (Catron) phenelzine dihydrogen sulfate (Nardil) and nialm Niamid) have rather suddenly burst into the scene all within the last 3 mon to a year On the one hand it has been said of them by some that they afford t best prophylactic treatment yet available for anginal pain, whereas on the othe hand serious hepatitis and hypotensive reactions have developed as a consequence of the use of Marsilid, the first of these to appear Others have suggested that the dangers attending their use are far greater than those indicated by these toxic reactions alone

Nothing is known of the way in which these drugs relieve patients with angina although it is clear enough that many of them obtain substantial prophylactic benefits A recent communication indicates clearly what had been in doubt before that the fact that these are monamine oxidase inhibitors is merely a coincidence and has nothing at all to do with the mode of their action in anginal patients One action which seems to be important has been established—the action on mood These are all "psychic energizers" (see Chapter 10) and provide a "lift" which in all probability elevates the threshold of awareness to disagreeable sensations (the pain of angina is characteristically associated with a sense of anxiety) arising as the result of deficient coronary circulation The hypotensive action of these drugs is far less likely to be an important element because (1) they are useless as continued therapeutic agents in hypertension and (2) the hypotensive action is a diffuse systemic one, and, should it develop to any significant degree, it would no doubt produce the same sort of collapse which marked the undesirable side reactions noted in the early use of Marsilid Some have claimed that grave danger exists in their use in anginal pain through the depressed awareness of, or concern with the painful warning which develops in insufficiency of coronary circulation

With these forebodings in mind it is only fair to repeat that the experience ith some of these drugs makes it clear that they may provide prophylactic relief hich is far superior to that provided by the nitrites On the other hand, until ore is known about the end results of the use of these drugs in coronar an extended period of time, it would be well to view them

and to use them only when acceptable relief cannot be provided by the nitrites. However, should it be proved that they are safer than the more cautious physicians seem to think, they will also probably be the most effective prophylactic medication for angina

Visammin (Khellin) —Visammin dilates blood vessels and has been shown to increase the flow of blood through the coronary arteries in the intact anesthetized animal In this action it is not so potent as nitroglycerin It has been reported, however, that it prevents the development of characteristic electrocardiographic changes which may develop during the exercise tolerance test in patients with coronary sclerosis, but it has not been demonstrated that khellin can dilate the sclerotic coronary artery No pharmacologic advantages over nitrite action have been demonstrated

At present, the clinical utility of khellin as a prophylactic is in dispute On the one hand, there are a number of clinical studies in which the regular use of this drug has been reported to provide complete relief in slightly more than half the patients with anginal syndrome and improvement in another third These observations, along with others on the effect of electrocardiograms in the exercise tolerance test and evidence that patients using khellin require less nitroglycerin than others, form the basis of the case for khellin On the other hand, in the study by Greiner and others, patients with angina were not able to distinguish between khellin and a placebo The drug is little used and as a matter of fact, is not even available in most pharmacies

Xanthines —The xanthine drugs—caffeine, theobromine, and especially aminophylline—have been extensively used over the years for angina Evidence of coronary artery dilatation rests on the demonstration in an isolated preparation that their use is followed by increased coronary flow and that in animals with ligated coronary arteries their use results in better healing of the infarcted area The former action is explained better by increased cardiac output than by coronary dilatation per se The latter contention was refuted by studies in which the size of infarcted areas in treated and untreated cats after coronary ligation was carefully measured under controlled conditions In addition, studies of the influence of xanthines on anginal pain in which the results were compared with those of placebo failed to reveal any difference between them

Although xanthines continue to be used in this condition, the amount prescribed is steadily decreasing A new member, choline theophyllinate, has been ushered into clinical use on the basis of poorly controlled studies which others have failed to corroborate It is not recommended here

SUMMARY —The present state of the xanthines in the relief of anginal pain is that as a group they provide little for the relief or prevention of an attack and that there is little in their known pharmacologic action on which to base such a hope

Thioureas —The thioureas, e g, propylthiouracil, have been used in the treatment of anginal syndrome While there have been reports of successes, many have had indifferent results It has been stated that the only indications for these drugs in patients with the anginal syndrome are for those with hyperthyroidism and as a test to determine whether euthyroid patients with the anginal syndrome will

as well as the fact that patients using them are also regularly instructed to carry nitroglycerin with them, 'just in case,' shows the uncertain confidence their proponents really have for their prophylactic utility

SUMMARY—The nitrites are pre eminently useful in the relief of the acute attack of anginal pain Here the rapid acting members far outstrip the others in satisfying the requirements The choice for this purpose depends on the convenience and ease of controlling dosage and application Usually, nitroglycerin is the choice On the other hand, where seconds or fractions of minutes are important, amyl nitrite is superior

The history of failures with so called long acting nitrites is an unbroken one From our understanding of the action of these drugs, such a quality is not within the province of nitrite action and should be sought in some other type of drug Since they could have no other useful attribute, no so-called long acting nitrite is the drug of choice in the anginal syndrome

Monamine Oxidase Inhibitors—A rather large group of agents belonging to this series, iproniazid (Marsilid), isocarboxazid (Marplan), β phenyl isopropylhydrazine (Catron), phenelzine dihydrogen sulfate (Nardil), and nialmide (Niamid) have rather suddenly burst into the scene, all within the last 3 months to a year On the one hand it has been said of them by some that they afford the best prophylactic treatment yet available for anginal pain, whereas, on the other hand serious hepatitis and hypotensive reactions have developed as a consequence of the use of Marsilid, the first of these to appear Others have suggested that the dangers attending their use are far greater than those indicated by these toxic reactions alone

Nothing is known of the way in which these drugs relieve patients with angina although it is clear enough that many of them obtain substantial prophylactic benefits A recent communication indicates clearly what had been in doubt before, that the fact that these are monamine oxidase inhibitors is merely a coincidence and has nothing at all to do with the mode of their action in anginal patients One action which seems to be important has been established—the action on mood These are all "psychic energizers' (see Chapter 10) and provide a 'lift' which, in all probability, elevates the threshold of awareness to disagreeable sensations (the pain of angina is characteristically associated with a sense of anxiety) arising as the result of deficient coronary circulation The hypotensive action of these drugs is far less likely to be an important element because (1) they are useless as continued therapeutic agents in hypertension and (2) the hypotensive action is a diffuse systemic one, and, should it develop to any significant degree, it would no doubt produce the same sort of collapse which marked the undesirable side reactions noted in the early use of Marsilid Some have claimed that grave danger exists in their use in anginal pain through the depressed awareness of, or concern with the painful warning which develops in insufficiency of coronary circulation

With these forebodings in mind it is only fair to repeat that the experience with some of these drugs makes it clear that they may provide prophylactic relief which is far superior to that provided by the nitrites On the other hand, until more is known about the end results of the use of these drugs in coronary disease for an extended period of time, it would be well to view them with circumspection

same salt of edathamil used in lead poisoning and that unless this one is carefully watched, it *provides a hazard of* hypocalcemic convulsions and death as well as of serious demineralization of the bones The results of this therapy, thus far reported, are discouraging

DESIGN FOR THE USE OF CORONARY ARTERY DILATORS

There are two important aspects of the therapy of anginal pain its relief and its prevention

There is the possibility that the myocardium suffers cumulative insults from the repeated episodes of hypoxia It is realistic, therefore, to attempt to alleviate each attack as promptly as possible and not to wait until it develops into a severe one which the patient treats when he can no longer tolerate the pain

The choice of the drug depends on the speed of relief desired Amyl nitrite is the quickest but is unpleasant in other respects, and since dosage is not limited it is more dangerous in the hands of the patient than fixed forms Nitroglycerin is only slightly slower but far more convenient It is safer than amyl nitrite since dosage is fixed It is usually the coronary dilator of choice

Relief with nitrite is an all or none proposition Therefore, the smallest dose which will relieve the pain is the proper dose Larger doses will provide no further relief but may induce undesirable side effects The best approach to dosage, therefore, is to start with the smallest possible therapeutic dose and work upward Such a procedure is feasible only when treating a patient with a history of repeated attacks For the single attack seen by the physician for the first time, amyl nitrite may be used until the pain is relieved

Prevention is quite another matter The nitrites are ineffective, and because of fundamental pharmacologic properties which are common to all thus far examined, it seems unlikely that any new nitrite will be any better

It should not be overlooked, however, that by the preliminary use of a nitrite it is possible to prevent a particular attack of angina when it seems likely to develop This prophylactic use of nitrites is not possible unfortunately, on a maintenance basis

Other drugs reputed to be effective coronary artery dilators are either ineffective or require re evaluation Until such evidence is available the only drugs which can be counted upon to dilate coronary arteries and relieve anginal pain are the nitrites

RATIONAL BASIS FOR NEW DRUGS

Many drugs are effective in angina what is clearly desirable and not so clearly available is a drug which prevents the attacks The persistent failure of nitrites to provide prophylaxis, presumably because of the development of tolerance, suggests that the search for still another nitrite is likely to be fruitless A drug of another pharmacologic group should be sought, one against which tolerance does not develop Since the useful action in the anginal syndrome is relief of coronary artery spasm by doses which do not dilate other vessels, it is a drug which has this particularized type of action and not another diffuse vasodilator which is needed

benefit by thyroidectomy They will not, therefore, be further considered here

Papaverine—Papaverine is a time honored arterial dilator but its record is unimpressive The consensus is that papaverine is not a useful drug in anginal syndrome

Dioxyline—Dioxyline (Paveril) is similar to papaverine not only in structure but in its pharmacologic and therapeutic actions as well It is not surprising therefore, that it is as ineffective as papaverine in relieving the anginal syndrome

Heparin and Bishydroxycoumarin—Recent studies have failed to confirm earlier suggestions that heparin and Dicumarol (bishydroxycoumarin) are of value in the prophylactic treatment of angina

Alcohol—It is commonly observed that alcohol in the form of spirit is of value in relieving anginal pain Although complaints of pain may decrease, there is no evidence that this improvement develops through dilatation of the coronary arteries It is a common practice to permit or even recommend alcoholic drinks for patients with angina pectoris Any beneficial action which may develop is probably due to the sedative action which reduces anxiety and makes patients less likely to expose themselves to the particularized stimuli which precipitate attacks

Vitamin E—The tocopherols have evoked considerable acrimonious dispute There is not a vestige of evidence adduced by way of well controlled study that they have any pharmacologic action which directly or indirectly might be useful for the anginal syndrome

Androgens and Estrogens—Clinical reports on the utility of androgens and estrogens in the anginal syndrome have conflicted There is no basis in laboratory experiment or theoretic knowledge for effective use of either of these agents in anginal pain Support in evidence of their utility has been poorly controlled Their use is fast waning

Nicotinic Acid—The well known flush which appears after nicotinic acid is used is due to dilatation of the cutaneous capillary bed There is no evidence that this effect is exerted in more deeply placed arterioles certainly no evidence clinical or otherwise supports the suggestion that nicotinic acid dilates coronary arteries

On the other hand the obvious effect of nicotinic acid is impressive to the patient and this may constitute strong suggestive therapy

Tissue Extracts—From time to time tissue extracts which exert a histamine like action are introduced as specific coronary artery dilators They invariably prove useless but their introduction continues The most fantastic of these are derived from cardiac muscle an obvious attempt at an irrational connection between the muscle used for making the extract and the site of its intended action

Calcium Chelators—Edathamil sodium (EDTA), a material which makes insoluble forms of calcium soluble and hastens their excretion has been used to dissolve kidney stones and abnormal calcium deposits in tissues and in dirty milk cans More recently it has been suggested that this action might be useful in the treatment of sclerosed coronary arteries Since these arteries do not react to nitrites such an effect would here be a valuable one

Until the utility of this procedure is established by carefully controlled experiment it must be considered to be an untested procedure Should one wish to apply this measure he should be aware of the fact that this is not precisely the

Gold H and Corday E Vasopressor Therapy n the Card ac Arrhythmias New England J Med 260 1151 1959
Kayden H J Bro l e B B and Steele J M Proca ne Am de—A Rev ew C rculat on 15 118 1957
MacMurray F G Stokes Adams D sease New England J Med 256 643 1957
S l erman L M and F chert H F Molar Sod u n Lactate Compared W h Elect al
Thom
W lso tl e Arrhythmias
Zoll I he Effects of External Electr c Currents on the Heart C rculat on 14 745 1956

Coronary Vasodilators

Anrep G V Kenway M R and Barsou n G S The Coronary Vasod lator Act on of Khell n Am Heart J 37 531 1949
Bra hfeld N Bozer J and Gorl n R Act on of N troglycer n on the Coronary C rcula t on n Normal and n M ld C rd ac Subjects C rculat on 19 697 1959
Cheval er H and S mon J The Management of Ang na Pector s Am Heart J 58 120 1959
Gold H Kw t N T and Otto H Xanth nes in the Treatment of Card ac Pa n J A M A 108 2173 1937
Goodman L S and G lman A The Pharmacolog cal Bas s of Therapeut cs ed 2 New York 1955 The Macm llan Co p 730
Gorl n R Brachfeld N MacLeod C and Bopp P Effect of N roglycer n on the Coronary C rculat on in Pat ents W th Coronary Artery D sease or Increased Left
Gre ner T
Heffel L B ol Chem 183 1 9 1950
Hefner L L Fr edman B Reeves T J Eddleman E E Jr and Harr son T R Sym
Melv lle logy n Med c ne 31/1
R seman of Ang na Pectons New
Sho hkes h, C C and Wach I F W Ipron az d n Ang na Pector s—A Double Bl nd Study C rculat on 20 17 1959
Traks E Hackel D B and Sancetta S M Effects of a New Coronary Vasod lator on the General and Coronary Hemodynam s and Myocard al Me abol sm of Man Ann Int Med 51 31 1959
Wegr a R Pharmacology of the Coronary C rculat on Pharmacol Rev 3 197 1951

When new drugs are presented for evaluation the tendency of anginal pain to subside spontaneously upon resting and of sedative drugs to reduce their incidence must be taken into account

SELECTED REFERENCES

Digitalis Materials

Bryfogle J W Santilli T Saltzman H A and Bellet S Therapeutic and Toxic Indexes of Digitalis New England J Med 256 767 1957
Cohen M D Digitalis Poisoning and Its Treatment New England J Med 246 225 254 1952
Cornell Conferences on Therapy Selection of Digitalis Preparations and Their Proper Administration Am J Med 13 883 1953
Ganz H F mo I D Intramuscular Administration & Med 95 349 1957
Gold, H 132 547 1946
Gubner J c ty by Chelation of Serum
Krantz J Cardiac Glycosides in Medical Practice Postgraduate Med 24 224 1958
Lown B and Levine S A Current Concepts in Digitalis Therapy New England J Med 250 771 1954
Lown B and Levine S A Current Concepts in Digitalis Therapy Boston 1954 Little Brown and Company
Lown B Wyatt N F Crocker A T Goodale W T and Levine S A Interrelationship of Digitalis and Potassium in Auricular Tachycardia With Block Am Heart J 45 589 1953
Marriott H J L Th 40 890
McGee R R an
Modell W Pearl Digitalis and Mercurial ent of Advanced Heart Failure Fed Proc 6 358 1947
Nalbandian, R M Gordon S Campbell R and Kaufman J A New Quantitative Digital Tolerance Test Based Upon the Synergism of Calcium and Digitalis Am J M Sc 233 503 1957

Cardiac Arrhythmias

Beckwith J R Ibarra J A and Wood J E Jr The Problem of Established Atrial Fibrillation Am J M Sc 231 519 1956
Bellet S Wasserman F and Brody J I Ef Card
Bettinger J of J Beat
Brill I C F men J C
Burrell Z L Chloroquine and Hydroxychloroquine in the Treatment of Cardiac Arrhythmias New England J Med 258 798 1958
Cattell McKeen and Gold Harry Relation of Rhythm to Force of Contraction of Mammalian Cardiac Muscle Am J Physiol 182 307 1955
Cohen B M Digitalis Poisoning and Its Treatment New England J Med 246 225 254 1952
Cohen B D Spritz N Lubash G D and Rubin A L Use of a Calcium Chelating Agent (NaEDTA) in Cardiac Arrhythmias Circulation 19 918 1959
Connolly D C Arrhythmias Associated With Digitalis Therapy Postgrad Med 25 509 1959
Cornell Conferences on Therapy Management of Disorders of Cardiac Rhythm Am J Med 5 110 1948
Duncan C H Stevenson I and Ripley H S Life Situations Emotions and Paroxysmal Auricular Tachycardias Psychosom Med 12 23 1950
Enselberg C D Treatment of Cardiac Arrhythmias A M A Arch Int Med 95 123 1955
Entwisle George The Cardiac Arrhythmias M Clin North America 39 1367 1955
Gold H Quinidine in Disorders of the Heart New York 1950 Paul B Hoeber Inc

chiefly rauwolfia alkaloids and salt restriction The condition may be suspected in patients above the age of 55 years with a high systolic pressure and a diastolic pressure below 100 to 110 mm Hg or, at an earlier age, when some other condition which predisposes to early arteriosclerosis such as diabetes prevails

Contrary to frequently expressed opinions, this type of hypertension tends to be labile, perhaps because the loss of arterial elasticity prevents the normal modulation of arterial pressure with changes in peripheral tonus and cardiac output Therefore, it is not uncommon to see extremely high pressures followed by relatively normal pressures a few hours or days later The condition denotes extensive arteriosclerosis and is probably associated with many of the accompanying vascular accidents such as cerebral lesions, coronary accidents aneurysmal dilatations and thrombosis of the large arteries to the extremities These complications, due largely to arteriosclerotic vascular disease, are often the cause of death of patients with arteriosclerotic hypertension Since the elevation of the blood pressure is secondary to the arteriosclerosis rather than its cause, there is usually little to be accomplished by blood pressure reduction or control in these individuals

Mild and Extremely Labile Hypertension—This is defined on the basis of wide random fluctuations in the blood pressure This condition is usually not associated with signs of vascular disease and is customarily considered an early form of hypertension Treatment is therefore generally of the more temperate variety In each case frequent recordings of blood pressure are necessary to arrive at an appropriate diagnosis and to establish intelligent treatment No evidence is available to show that any of the antihypertensive drugs reduce lability of blood pressure but they may by lowering the basal value, reduce the maximum blood pressure reached at peak levels This may be of practical value in preventing attacks of left ventricular failure or severe hypertensive headaches due to acute rises in blood pressure It is possible but not proved, that the reduction of frequent surges of hypertension will delay the onset of more serious complications of the disease

Established Hypertension Without Complications—This is the form of the disease which offers the greatest difficulty in the selection of drugs for treatment On the one hand, many patients live the normal life span without injury to target organs while in others this stage is merely a brief prelude to a fatal termination If one were able to determine the prognosis, one might decide whether mild or vigorous treatment is the more desirable

It is the general experience that particular prognostic features are ominous and when present, should guide the therapist to more vigorous treatment even when the disease appears to be benign Among these are (1) youth, (2) high diastolic pressure, (3) male sex, and (4) the Negro race

In addition to these general considerations, prognosis is dependent on the progressive elevation of blood pressure or on changes in heart, brain, or kidneys For this reason, a careful record of blood pressure readings as well as of target organ disease should be kept in every case Complications which tend to indicate a serious prognosis follow in approximate order of severity (1) progressing renal failure, (2) the development of hemorrhages or fresh exudates in the retina, (3) cardiac failure as evidenced by history, or cardiac enlargement, (4) cerebrovas

THE CHOICE OF DRUGS IN THE TREATMENT OF HYPERTENSION

Sibley W Hoobler, M D

INTRODUCTION

The choice of drugs in the treatment of hypertension is not easy In the first place, it is not sufficient to make a diagnosis of hypertension one must take the stage of the illness and its prognosis into account before selecting drugs In the second place, the drugs used in this disease are not uniformly effective or free from unpleasant side effects Consequently, one must weigh the therapeutic benefits to be achieved against the side effects produced by these agents In the third place, hypertension is a chronic disease in which no drug is curative, and all treatment must be considered as suppressive thus, any agent used for hypertension must be considered in terms of a lifetime procedure This means that more than usual care must be taken in selecting the agent to be used and in measuring its effects on the blood pressure In the fourth place, the mechanisms of hypertension are so poorly understood that the effectiveness of treatment is evaluated largely by evidence of a reduction in blood pressure, a criterion which is not easy to establish in a disease notable for spontaneous fluctuations

CLINICAL APPLICATIONS

Table 25 presents the various categories of hypertensive disease The general type of treatment recommended for each condition depends on the prognosis

"Curable" Forms of Hypertension —Certain forms of hypertension may be cured by surgery This text does not cover such aspects of hypertensive disease, but the reader should always consider the possibility of *unilateral renal lesions, Cushing's disease, primary aldosteronism,* and *coarctation of the aorta* Although an *adrenal medullary tumor* is an exceptional cause of hypertension, it is often wise also to exclude this possibility by appropriate pharmacologic testing

Arteriosclerotic Hypertension —This represents a category in which inelasticity of the aorta and large vessels gives rise to a higher than normal systolic pressure during ventricular systole There is no increase in the resistance of the arterioles and consequently the diastolic pressure remains near normal limits This condition is generally benign and, therefore, treatment should be of a mild variety involving

Low Fat Diets These have also been recommended but, in addition to doubt concerning their efficacy in preventing vascular atherosclerosis, they have no specific value in treating the blood pressure per se

Weight Reduction Such a program has its place in relieving cardiac work, but it is doubtful that, apart from the apparent improvement which comes from measuring the blood pressure on a thinner arm, there is actual reduction in blood pressure

VASODILATORS —The *nitrates* and *nitrites*, *theobromine derivatives*, and *nicotinic acid* have been largely replaced by more potent agents The nitrites may have specific use in the treatment of angina pectoris accompanying hypertension but are not useful in the treating of the blood pressure per se The *thiocyanates* have been demonstrated to produce a slight reduction in blood pressure only in the milder forms of hypertension

RAUWOLFIA —Rauwolfia in crude and purified forms lowers the blood pressure moderately but continuously in about 50 per cent of cases of mild and moderately severe hypertension Since it is usual for the blood pressure to fall spontaneously as the patient and physician develop a degree of rapport, it is important to distinguish this from the specific effects of rauwolfia Since treatment is expensive it is distinctly worth while to establish whether the drug is producing the blood pressure reduction Consequently, a control period of blood pressure readings with nonspecific treatment is useful If this is not practical, it is advisable to have readings of both blood pressure and pulse rate at least every 2 weeks during drug therapy The patient is given 0 25 mg of reserpine or its equivalent 3 to 4 times daily for at least 2 months and the dosage increased if side effects permit and the pulse rate does not slow At the end of 8 to 10 weeks, blood pressure reduction should reach a maximum If it seems significant when compared with the starting blood pressures the total daily dose may be reduced to 0 25 mg daily and the patient advised to continue with the drug indefinitely If the patient, who has been treated with rauwolfia by another physician, experiences a rise in blood pressure and pulse rate after 3 to 4 weeks of treatment withdrawal, the indications are that the drug has been helpful and should be reinstituted

Among the more important side effects of rauwolfia are a tendency to gain weight, occasional formation of edema, and the development of nasal stuffiness (often prevented by combining the drug with an antihistaminic) Serious mental depression may occur at any time This should be watched for and both the patient and a relative warned of the possibility Frequently, it makes its appearance as an apathetic or agitated reaction but sometimes as an excessive reaction to a normally depressing experience It is important to remember that the effects of rauwolfia wear off slowly and that it may be several weeks before recovery from the depression is complete If this complication is constantly watched for no serious risk is entailed, but this is nevertheless the major danger of therapy with this agent

PARENTERAL RESERPINE —This is a useful method to treat emergencies in which prompt blood pressure reduction is needed (subarachnoid hemorrhage, impending hypertensive encephalopathy, convulsive encephalopathy of renal disease or toxemia of pregnancy, or acute anxiety states accompanied by severe hyper

Table 25 Classification of Hypertension in Terms of Therapeutic Needs
4 Secondary Forms of Hypertension

Type	Definition	Diagnostic Sign or Procedure	Frequent Clinical Findings	Prognosis Without Treatment	Treatment Objective	Treatment Technique
Curable	Unilateral renal	Intravenous pyelogram	None characteristic	Serious	Normal BP	Nephrectomy
	Cushing's disease	Hydroxy and ketosteroid excretion	Hyperglycemia characteristic obesity etc	Serious	Normal BP	Adrenalectomy
	Hyperaldosteronism	Low serum potassium	Weakness polyuria	Moderately serious	Normal BP	Adrenalectomy
	Coarctation	Lower BP in legs than arms	Young persons systolic murmur	Serious	Normal BP	Resection of coarctation
	Pheochromocytoma	Histamine or Regitine test*	Vasomotor attacks	Serious	Normal BP	Adrenalectomy
Arteriosclerotic	Age over 55 or diabetic diastolic BP 110 mm Hg or less	None	Arteriosclerotic complications	Moderately serious depends on locus of atherosclerosis	Moderate BP reduction	Rauwolfia chlorothiazide SBA† rarely advised in cerebral insufficiency anticoagulants if BP kept <200 mm systolic
Toxemia of pregnancy	High BP and albuminuria with onset or increase in last trimester	Clinical diagnosis	Edema excess weight gain	Variable	(1) Many hypertensive women without complications can carry pregnancy safely under close supervision (2) Terminate pregnancy after three weeks of uncontrolled toxemia	(1) Prophylactic or therapeutic (a) Extreme salt restriction (200 mg Na diet), chlorothiazide and rauwolfia (2) Veratrum if necessary in addition to keep BP below 160 mm systolic
Acute nephritis	Hematuria, albuminuria edema	Clinical diagnosis	Edema retinopathy heart failure azotemia BP labile	Variable	BP control only as necessary to prevent or relieve encephalopathy	(1) Magnesium sulfate I M (especially in children) (2) Rauwolfia parenterally (3) Veratrum or SBA if necessary

*See Chapter 42 on Diagnostic Tests
†SBA—sympathetic blocking agents When these are ineffective, sympathectomy may be advised in cases of

Table 26 *Comparative Action and Uses of Various Ganglionic Blocking Agents**

Generic Name	*Dosage and Duration*	*GI Absorption*	*Renal Excretion*	*Characteristic Side Effects‡*	*Preferred Clinical Indications*	*Remarks*
(a) Tetra ethyl ammonium Cl	*Parenteral* I V 200 300 mg not advisable for continuous infusion, lasts 20 30 min	------	Complete	Paresthesias, brief BP rise precedes fall	(a) Provocative test for pheochromocytoma when BP normal (b) Differential diagnosis of headaches due to high BP	(1) Increased effect in elderly and azotemics use smaller dose
	Oral Ineffective	None	------	------	------	------
(b) Trimethaphan camphor sulfonate	*Parenteral* † 4 20 mg I V per min by infusion lasts 5 20 min	------	Partial	Flushing, hyperpnea nausea with overdose	(a) For rapid, precise BP control in emergency (b) Used in hypotensive anesthesia	(2) Has mild direct vasodilator as well as ganglion blocking action, this drug by infusion requires constant supervision
	Oral Ineffective	------	------	------	------	
(c) Hexamethonium	*Parenteral* † I V 1 50 mg for rapid effects on BP, 2 5 25 mg subcutaneously every 4 hr, lasts 2-4 hr	------	Complete	------	(a) Parenterally, for initial control of BP in hypertensive emergencies	(3) Chronic oral use has been replaced by longer acting drugs
(d) Pentolinium	*Parenteral* † 0 5 10 mg I V as in (c), 1 15 mg subcutaneously every 6 hr, lasts 4 6 hr	------	Complete	------	(a) Parenterally, for longer action in control of BP	
	Oral 25 150 mg 3-4 times daily, lasts 5 7 hr	5 15% dependent on intestinal motility	Complete	------	------	(4) Dosage after toleration may have to be increased

tension) A single dose of 2.5 to 5.0 mg may be given intramuscularly and repeated every 4 to 6 hours for several days. Maximal vascular effects appear in 30 to 60 minutes along with sedation, flushing, and other characteristic side effects. The blood pressure falls at least to the usual level for the patient and often may reach near-normal values. Shock, postural hypotension, ileus and urinary retention which may accompany emergency treatment with ganglionic blocking agents, are not caused by reserpine. It is particularly useful for treatment in the home where continuous supervision of blood pressure to avoid excessive hypotension is not feasible. The safety of this treatment is attested by its wide use in mental hospitals in much larger doses than recommended here. Such larger doses rarely produce greater blood pressure reductions than the 5 mg dose.

CHLOROTHIAZIDE.—This drug is the treatment of choice for mild hypertension and as an adjuvant to other regimens. See more extensive discussion on page 453.

Potent Treatment Regimens.—

HYDRALAZINE.—Apresoline (hydralazine) is recommended as a hypertensive drug which dilates vessels generally. It also increases cardiac output and has a general excitatory effect on the circulation. However, hydralazine alone rarely lowers the blood pressure significantly for more than a short period.

Its use is attended by many side effects, some of them most distressing to the patient, among which are severe generalized headache, palpitation, tachycardia, edema, nausea, vomiting, chills, and fever. Early in treatment, joint pain and an influenza like syndrome suggesting serum sickness sometimes develop. A more serious late manifestation of hydralazine treatment, occurring after 6 months or more of therapy, is a lupus erythematosus-like syndrome with arthritis, fever, malaise, positive lupus erythematosus cell phenomenon, abnormal cephalin flocculation, and leukopenia. In most cases, the syndrome subsides on discontinuing treatment. Cortisone may, however, be necessary. This syndrome is partially but not entirely related to dosage. It is uncommon when the total daily dose of Apresoline is below 200 mg.

Many experienced physicians use the drug in combination with reserpine or in combination with ganglionic blocking agents, which, while minimizing some of the hydralazine side effects, add others. It is my opinion that the drug rarely offers sufficient promise to justify its general use. On the other hand, it is the experience of some of the more enthusiastic supporters of this treatment that over a period of several months there is a gradual reduction in the requirement for the more potent ganglionic blocking agents, if hydralazine is combined with them in the treatment program. This claim, however, requires substantiation, but if it were established it would indicate an important quality of this agent. The contraindications for hydralazine include angina pectoris and peptic ulcer, which may be aggravated by the cardioexcitatory and the stimulant effect on gastric secretion.

VERATRUM ALKALOIDS.—These agents unquestionably lower the blood pressure and are quite safe, but they also cause nausea and vomiting. When used intravenously or parenterally for short periods, blood pressure reduction can be achieved without emetic side effects, but in long-term oral use there is such a narrow margin between these effects that blood pressure red...

the cost of suffering nausea or vomiting 2 or 3 times a week These are not the drugs of choice for the management of hypertension

For many years, veratrum has been used parenterally in the treatment of toxemia of pregnancy This is probably an effective sphere of usefulness, for the parenteral administration of the drug may lower the blood pressure quickly and sustain the effect for the short period before delivery

The side effects of veratrum treatment include paresthesias in the throat and perioral region, nausea, and anorexia In addition, at the peak of drug action there may be vomiting and extreme hypotension

The effects on heart rate and rhythm are dramatic There is, first of all, a pronounced bradycardia, sometimes followed by varying degrees of heart block and of idioventricular rhythms Despite the ingestion of massive doses, however, very few serious effects have been reported Bradycardia and rhythm disturbances may be promptly stopped by the intravenous administration of 1 mg of atropine sulfate This should always be at hand when the drug is given by the parenteral route Since at least some of the blood pressure reducing effect is due to a decrease in cardiac output the increase in rate and the rise in output following atropine usually raise the blood pressure somewhat If the rise is insufficient, it may be increased with such pressor agents as Neo-Synephrine and norepinephrine

Heroic Treatment Regimens Sympathetic Blockade.—

GANGLIONIC BLOCKING AGENTS —These agents lower the blood pressure in the great majority of hypertensive individuals It appears that they do so by reducing cardiac output rather than by a major decrease in total peripheral resistance Their effectiveness in lowering blood pressure is the chief argument in favor of their use when vigorous treatment is necessary Full advantage should be taken of the postural fall in blood pressure and the patient should be treated until the standing systolic blood pressure becomes as low as tolerable If this can be kept in the range of 110 to 150 systolic,* it is not likely that the effects of high blood pressure on the vessels will be serious, and further progression of the disease will be prevented At the same time, syncopal effects will be avoided if the pressure is kept above the level of 110 mm Hg

Since such fine control is rarely possible without strict monitoring of the blood pressure, patients on this program are advised to record their own blood pressure on a chart and bring it with them to the doctor's office for review In opposition to the generally accepted feeling that the patient should not know much about his blood pressure, I have found that this program actually breeds confidence on the part of the patient that the disease is really under as good control as is possible It is only the exceptional person who becomes a "blood pressure neurotic" on this program, whereas the uncertainty of not knowing the blood pressure or of trying to guess the blood pressure from symptoms or from the physician's attitude has indeed caused much anxiety

*Systolic blood pressure falls more than diastolic and is easier to determine, while the relationship of systolic to diastolic and recumbent to standing blood pressure cannot be materially altered by changing the dosage of the drug For the purpose of simplifying control programs, therefore the systolic blood pressure reading is stressed as the more likely to indicate impending syncope

(e) Chlorisondamine	*Parenteral* † 0.5–10 mg IV as in (c), 1–10 mg subcutaneously 2–3 times daily, lasts 5–7 hr		Complete	Mydriasis prominent	(a) For long-acting parenteral effect especially in cases with critical renal function	
	Oral 25–150 mg 2–3 times daily, lasts 6–8 hr	10–20% variable as in (e)	Complete	Mydriasis prominent	(b) Second choice when mecamylamine causes undesirable side effects	(5) Mydriasis often affects ability to work; treat with 1% pilocarpine eye drops, tinted glasses and refractive correction
(f) Mecamylamine	*Parenteral* † 2.5–10 mg IV or IM, rarely used because onset of action delayed 30 min or more, lasts 7–10 hr		Partial; greater excretion when urine is acid			(6) Complete oral absorption, slow onset and long duration of action, less retention in renal failure, less tolerance and fewer side effects make it drug of choice
	Oral 2.5–30 mg 2–3 times daily, lasts 8–12 hr or more	Complete	Partial as above	Coarse tremor in patients with renal insufficiency or cerebral arteriosclerosis occasionally seen	(a) Preferred oral ganglionic blocking agent	(7) If control ineffective, trimethidinium or chlorisondamine is next choice
(g) Trimethidinium methosulfate	*Oral* 20–100 mg 3 times daily	Partial	Complete	Mydriasis	(a) Preferred when constipation, dry mouth severe with other ganglion blockers	(8) Fewer parasympathetic blocking effects

*Sympathetic blocking drugs, not tabulated here, described in text.
†Initial trial dose should always be small to exclude hyperreactors. Patient should also receive chlorothiazide 500 mg twice daily.
‡Other than those of general autonomic blockade as described in text.

less effective than mecamylamine causes more mydriasis and exhibits greater variation in day to-day absorption

Other side effects can be only partially relieved *Pilocarpine eye drops* sometimes improve the visual symptoms, but when the treatment has been stabilized refraction and the prescription of *new glasses may be the only* measure of value to those seriously disabled by this complication Dizziness re lieved by recumbency is usually a sign of excessive action of the drug or that the blood pressure is being lowered beyond the patient's vascular tolerance In this situation, the dosage is reduced For impotence, temporary cessation of the drug may be effective Although prolonged withdrawal of these agents may result in serious hypertension, cessation for 2 to 3 days will not be as serious as some of the complications which might follow the continued use of these drugs in the face of serious side effects Blood pressure should be followed with particular care when the drugs are stopped since this will demonstrate the advent of a potentially dangerous hypertensive rebound

Parenteral Use The parenteral use of ganglionic blocking agents may be in dicated (1) in acute hypertensive crises and (2) in the more precise control of blood pressure in patients with impending renal failure in which reduction must not be excessive for fear of aggravating azotemia Since most ganglionic blocking agents may be given intravenously or subcutaneously with similar but more dependable effects than by the oral route, this form of treatment is often the desirable one

For the hypertensive emergency not responsive to reserpine other paren teral treatment is necessary Intravenous infusion of trimethaphan (Arfonad) at *the rate of 4 to 20 mg per minute with constant supervision of blood pressure will* bring about a prompt fall that is reversible The rate of infusion can be used *to control the degree of blood pressure reduction If symptoms do not improve*, the restoration of hypertensive levels is rapid on discontinuing treatment

Another *method for treating the emergency* case involves the intravenous ad ministration of hexamethonium to the patient in the sitting position at the rate of 1 mg per minute until a blood pressure reduction halfway to normal *levels is* achieved or until 50 to 75 mg of the agent has been given It is extremely im portant that the blood pressure be checked every minute during this treatment and that overdosage be avoided

If more gradual blood pressure reduction is desired it may be sufficient to give hexamethonium subcutaneously every half hour, beginning with a dose of 2 5 mg (to exclude the extremely sensitive case) The dose is then increased to 5 10 and 20 mg at successive half hour intervals until the *blood pressure has reached* a point halfway between its previous level and normal Comparable parenteral doses of pentolinium (Ansolysen) or chlorisondamine (*Ecolid*) *are* 1 2 4 and 8 mg Maintenance doses of these agents every 4 to 6 hours will sustain the blood pres sure *reduction for the first several days of inpatient* treatment until the patient can be placed on an oral regimen

Selective Sympathetic Blockade —Bretylium tosylate (Darenthin) *is repre sentative* of a new class of sympathetic blocking agents which are said to prevent release of norepinephrine at sympathetic nerve endings without producing postural tachycardia and parasympathetic or ganglionic blockade They do not *inhibit the*

Sensitivity to Ganglionic Blocking Drugs Factors which may increa sensitivity to ganglionic blockaders are (1) colds and infections often of a tively innocuous variety (2) salt and water loss in hot weather or following retics (3) alcohol or other vasodepressors (which may include reserpine, nitr antihistaminics and chlorpromazine) (4) excessive muscular exertion (5) creased cerebrospinal pressure (as in acute encephalopathy and subarachnoid hemo rhage) (6) sympathectomy and (7) the vasodilator effects of large meals

Since sympathetic activity is at its minimum in the early morning if the pa tient is under continuous blockade, very low standing blood pressures are not uncommon on awakening The standing pressure tends to rise toward evening despite equal blockade It may be necessary to raise the dose of the drug to counteract this Consequently the blood pressure should be taken in the morning on standing and the dose arranged for the day on the basis of this reading The blood pressure is next recorded in the evening Occasionally patients will get into difficulties after luncheon particularly if it is a large one or if there is unusual absorption of the morning dose Appropriate adjustments in this regimen as well as constant vigilance are therefore, necessary for the best control

Side Effects Severe side effects are the most important contraindication to increasing the dosage These are inevitable when ganglionic blockade is achieved and include in increasing order of importance visual difficulty anhydrosis dry mouth difficulty in voiding nocturia progressive renal failure in patients with borderline renal azotemia and finally constipation progressing to ileus With adequate blockade impotence is to be expected in most male patients

Of these side effects only progressive azotemia and obstipation with ileus are to be feared The former may be prevented by very cautious blood pressure reduction in patients with elevated nonprotein nitrogen levels and by avoiding treatment in those with renal azotemia exceeding 100 mg per 100 ml It has been my experience that it is impossible to predict the renal effects of ganglionic blocking agents in mild azotemia Usually there is an initial slight rise which is ignored provided it is not progressive and which tends to disappear within 10 to 14 days n these patients one lowers the standing blood pressure about halfway to normal d attempts further reductions only when the nonprotein nitrogen level is stabi d

To prevent ileus insistence on daily use of stimulating laxatives during initiation of treatment combined with the strict requirement that 48 hours with bowel movement be an indication for stopping treatment has prevented serious lications There seems to be no difference between laxatives I recom the less expensive forms irritant fruit juices milk of magnesia and cascara Phenolphthalein derivatives and effervescent salts are sometimes more ful Bulk laxatives should be avoided since they may further reduce the contents through the already paretic bowel Prostigmin is expensive and icularly useful by mouth but it is of unquestioned value parenterally in ment of a drug induced ileus

n constipation is troublesome trimethidinium (Ostensin) may be s cording to the schedule in Table 26 This quarternary r effect on parasympathetic than on sympathe

sented with potassium chloride or fruit juice supplements, and by spacing the doses at 12-hour intervals After reduction *in fluid volume a self limiting mechanism as yet not understood, prevents further fluid depletion* Ingestion of moderate amounts of sodium chloride (2 to 4 Gm) daily does not overcome these effects although a greater intake will result in salt repletion and cancellation of the physiologic effect of chlorothiazide Cessation of treatment may result in an abrupt rise of blood pressure discontinuance of this medication therefore demands careful supervision

A quite regular effect is observed when chlorothiazide is used in conjunction *with sympathetic blocking agents It may reduce the requirement for these drugs* by 50 per cent in most patients It also potentiates the effects of sympathectomy so that patients who have previously responded poorly to surgery now exhibit significantly reduced blood pressure levels The sensitizing effects of chlorothiazide are similar to those described when a mercurial diuretic is given to a hypertensive patient who is receiving a ganglionic blocking agent

In view of this fact, patients are now given ganglionic blocking agents only *after 3 days of chlorothiazide therapy If blockade has been established blood pressure* may fall a few hours after adding chlorothiazide In such cases therefore the level is carefully watched and the dosage of the ganglionic blocking agent is promptly reduced when necessary The effect is retained with maintenance dosage (0 5 Gm twice daily)

Potentiating effects of this drug in combination with other antihypertensive agents, hydralazine, reserpine, and veratrum, have also been reported It has not *yet been established, however, whether the blood pressure reduction reported for* such combinations is additive or synergistic Until more information is available, there appear to be no reasons why such combinations should not be tried

For the present, my preference is to use chlorothiazide with or without reserpine in mild to severe hypertension without complications, after sympathectomy and whenever there is an indication for the use of *sympathetic blocking* agents If the drug is to be effective in a particular patient, careful observations of blood pressure will establish this fact within a few days or a week prolonged therapeutic trial or precise dosage adjustment are not necessary In an occasional refractory case a temporary increase in daily dosage to 2 to 3 Gm may produce the desired response, but it has been established that prolonged administration *of doses* in excess of 1 Gm daily is unnecessary

There are no reports of serious toxic effects due to chlorothiazide Potassium depletion and aggravation of azotemia seem the most likely dangers Therefore potassium should be given orally, whereas in patients with severe azotemia the drug is given carefully In hypertensive patients with cardiac disability, the drug *would* appear to be potentially of great value, but if digitalis is being taken potassium depletion should be avoided *The effect of the drug on the* cerebral complications of hypertension has not been determined, but severe hypotension and dehydration should not be induced in patients liable to cerebrovascular thrombosis

The dangers of cumulative toxic effects have not yet been established *Chlorothiazide* seems safe and there are no present, clear contraindications or special warnings other than that the physician should carefully and *conscientiously* follow

effects of epinephrine and its congeners on the peripheral vessels and thus may be differentiated from dibenamine like compounds

Clinical experience with these drugs is at present very limited, and it is difficult at this time to predict their usefulness Over a period of several months Boura and collaborators have reported no evidence of toxicity A brief experience indicated that orthostatic normotension can be produced in most hypertensive subjects by doses of 200 to 600 mg 3 times daily with meals that overdosage or increased repsonsiveness may lead to postural hypotension with symptoms of lightheadedness syncope or weakness and that as with ganglionic blocking agents recumbent hypertension is little affected by doses sufficient to reduce standing blood pressure readings to normal However the disabling effects of parasympathetic blockade are absent It is probable that improved derivatives will soon become available One long acting compound guanethidine has been described which unfortunately causes diarrhea in some patients As might be expected the effect of these adrenergic blocking agents is potentiated by chlorothiazide which should therefore be prescribed concomitantly

DRUGS OF CHOICE —For reasons outlined in Table 26 of all the ganglionic blocking agents my preference is for mecamylamine (Inversine) Its regular and dependable absorption from the gastrointestinal tract makes oral administration feasible and safe After good bowel activity has been secured this agent is given in dosage of 2 5 mg, 2 to 3 times daily increasing by increments of 2 5 mg every day while in the hospital or every third day on an outpatient basis until the blood pressure is at a desired level or the side effects of parasympathetic blockade become intolerable It is estimated that with great care in supervision there will be satis factory blood pressure reduction without intolerable side effects in approximately 80 per cent of patients on this regimen The selective sympathetic blocking agent bretylium may after more experience be proved superior to mecamylamine

Chlorothiazide—The introduction of the orally effective diuretic and salu tic drug chlorothiazide (Diuril) has provided a new tool for the management r hypertension This agent related to sulfanilamide appears to inhibit the renal absorption of water, sodium chloride, and to a lesser extent potassium by chanisms which resemble both those involved in the diuretic actions of aceta amide Diamox) and the mercurial diuretics In an extensive experience narkably few toxic effects have been reported Patients without edema who t this drug exhibit weight loss with some degree of asthenia Rare toxic effects ude skin reactions thrombocytopenia and jaundice When the drug is used e a moderate antihypertensive effect has been observed in from one fourth to half of cases with milder forms of the disease when salt is avoided When the rtension is associated with occult or manifest edema particularly in patients ing steroid hormones reduction of blood pressure is more frequent n the nonedematous subject a loss of 2 to 4 pounds can be expected when is administered twice daily for 1 to 3 days This is due to reduction in plasma and extracellular fluid The effect on the blood pressure corresponds to pected in patients with essential hypertension subjected to a 200 mg sodium The fluid depletion produced by the chlorothiazide may be maintained with twice daily Serum potassium levels may decline but this can be pre

out his life using home, not office blood pressure, as a measure of adequate control Regression of vascular lesions must be a further measure of effectiveness

Reduction in blood pressure taken at home must be continuously demonstrated * Such a reduction must exceed 20 to 40 mm pressure from the untreated level the systolic standing blood pressure at all times should remain below 180 to 190 and should preferably be below 150 If these stipulations are not met it is doubtful that chronic suppressive treatment will be worth while

It should be stressed that management of hypertension is chronic and long continued and the patient should never remain for long periods away from the physician s observation since this may result in interim rises in blood pressure of considerable degree unknown to the patient and, therefore, untreated by the physician There is a common but fallacious hope among hypertensive patients that once a blood pressure reduction apparently has been secured by a particular regimen the treatment plan never needs revision Nothing could be farther from the truth The disastrous experience of occasionally discharging a patient on a simple treatment program only to find him some years later with severe hypertension and hypertensive encephalopathy has convinced me that once the hypertensive patient requires treatment he also requires frequent re examination at least at 3 to 6 month intervals throughout the remainder of his life

RATIONAL BASIS FOR NEW DRUGS FOR THE TREATMENT OF HYPERTENSION

The criteria of an ideal antihypertensive agent may be summarized as (1) complete oral absorption, (2) persistent effects (3) action at the site of the deranged vascular mechanism by relaxing arteriolar constriction and (4) no tendency to tolerance It is apparent that no drug presently available fulfills the criteria of a successful to say nothing of this ideal antihypertensive agent and that increasing the potency of agents with the pharmacologic properties of those presently available will not lead to it

While the rauwolfia alkaloids satisfy some of the criteria there is no evidence that they act directly on the constricted arterioles Furthermore, they are not sufficiently potent to be effective in cases of great severity The evidence that reserpine acts by depleting serotonin and that an antagonist to serotonin is no more effective than reserpine in lowering blood pressure indicates that more potent reserpine like agents will probably not have greater effectiveness

With the possible exception of mecamylamine, patients develop tolerance to the ganglionic blocking agents These drugs do not have the desired site of action Although it is still controversial most authors agree that cardiac output is reduced by them Blood pressure reduction based on this mechanism is not desirable It would appear that the effectiveness of ganglionic blockers has reached its peak with mecamylamine which is completely absorbed and has persistent action with side effects that are frequently tolerable

*Occasionally it is well to advise a therapeutic vacation during which the blood pressure is followed This will demonstrate to patient and physician whether there s any value to the treatment and at the same time dangerous rebound will be prevented if the drug is immediately resumed should blood pressure rise excessively

current reports of medical experience with this interesting and effective diuretic agent

A number of chlorothiazide derivatives (e g, hydrochlorothiazide, flumethiazide) have been recommended in preference to the parent drug usually on the basis of lesser kaluresis The differences are not of great clinical significance Skin reactions and thrombocytopenia from chlorothiazide may sometimes be avoided by changing to these newer derivatives [There is no reason however, to believe that similar reactions cannot also develop as the result of the use of these newer derivatives of chlorothiazide Ed]

A DESIGN FOR THE USE OF DRUGS IN THE TREATMENT OF HYPERTENSION

My general philosophy of the treatment of hypertension involves the use of three established agents in the management of various forms of hypertension—chlorothiazide rauwolfia alkaloids, and mecamylamine

The First Choice —In patients in whom relief is not urgent, chlorothiazide 0 5 Gm twice daily, is first used for a period of 2 to 3 months If blood pressure can clearly be shown to be reduced by this treatment to levels below about 180/110, the author does not proceed to more complicated treatment programs If the response is inadequate, reserpine 0 25 mg 3 times daily for 2 months, may be given followed by a maintenance dose of 0 25 mg per day

The Second Choice —Should this program fail to affect the blood pressure, there is little evidence that its continued use is helpful A decision must then be made whether or not the patient belongs in the category of hypertensive disease which justifies more vigorous treatment with ganglionic blocking agents in addition to chlorothiazide In this decision the age of the patient the sex and race the evidences of progression of the disease, particularly as found in the search for the vascular complications mentioned in Table 25, are weighed to determine whether more vigorous treatment is desirable If it is decided to use a ganglionic blocking agent, the patient is instructed in self determination of the blood pressure,* a suitable 2 to 4-week base line of standing morning and early evening blood pressures is recorded chlorothiazide and cathartics are given routinely, and mecamylamine is started in increasing doses until there is satisfactory blood pressure reduction or until despite a daily laxative, distention or obstipation is intolerable

If treatment is attended by too many side effects but is still necessary, the following steps are considered (1) addition of reserpine or hydralazine to the program in an effort to permit reduction of dosage and side effects of ganglionic blocking agents (2) conversion to trimethidinium or bretylium tosylate (3) sympathectomy, and (4) if the latter is unsuccessful reversion to chlorothiazide, reserpine and ganglionic blocking therapy since after sympathectomy patients tend to exhibit increased sensitivity to such a program Three guiding principles are followed The prognosis of the disease must justify the introduction of the side effects of the treatment The patient must expect continued supervision through

*Sphygmomanometers designed for this purpose are available from the Propper Manufacturing Company

THE CHOICE OF VASOCONSTRICTOR DRUGS FOR HYPOTENSION AND SHOCK

John H Moyer, M D, and

Lewis C Mills, M D

INTRODUCTION

The primary purpose for the systemic administration of vasoconstrictor drugs is to increase arterial blood pressure It is quite obvious that the most effective method for treating severe hypotension, whether or not it is associated with other clinical manifestations of shock, is to correct the underlying disease responsible for the reduction in blood pressure However, it is not always possible to correct the cause of the hypotension immediately Under these circumstances it may be lifesaving to maintain the blood pressure artificially for variable periods of time so that an adequate supply of blood may continue to flow through the brain and other vital vascular beds

There are a number of patients in shock, particularly those with medical complications, who do not respond to the administration of fluids or blood transfusions Indeed, fluids may sometimes be contraindicated Even when the shock is due to hemorrhage and other surgical causes, vasopressor agents may prove to be valuable as a temporary expedient either to maintain blood pressure until blood can be replaced or as a supplemental measure in those patients who do not obtain a prompt and adequate response to blood and fluid administration

PHARMACOLOGIC CONSIDERATIONS

General Considerations —Vasopressor agents should restore systemic blood pressure quickly and should direct circulating blood to the more vital vascular beds which are critical for life, it is of primary importance that the circulation be maintained through the brain the heart the liver, and the kidneys In maintaining the circulation it is essential that this not be brought about by stimulating the heart and increasing cardiac output only, else cardiac complications may follow For example, epinephrine is useless in man when used as a vasopressor agent since the primary effect is on the myocardium, increasing cardiac output, and at the same time having very little constrictive effect on the peripheral vessels unless ex

The ideal drug should relieve the excessive vasoconstriction at the arteriole rather than reduce blood pressure, even in part, by decreasing cardiac output From this standpoint, hydralazine and the nitrites exert a desirable effect Unfortunately, hydralazine does not act in all cases, and when it does, it produces many undesirable side effects Furthermore, there appears to be a stimulation of cardiac output which is clearly undesirable

The nitrites and other direct-acting vasodilators unfortunately act on smooth muscle of veins as well as of the arterioles and it is probable that a decrease in cardiac output also plays a role in their action This is deduced from the fact that postural hypotension frequently develops following their use, suggesting that the effect on venous tone and reduced cardiac output are factors in the blood pressure reduction Furthermore, tolerance develops rapidly

One would imagine that a sympathetic blocking agent which does not have parasympatholytic properties would be of greater value since at least the distressing side effects of parasympathetic blockade would be avoided Dibenamine-like compounds which, like phentolamine, do not block the cardiac sympathetic innervation have side effects of postural hypotension and tachycardia which are most undesirable Bretylium tosylate, a recently introduced agent, avoids these objections, but in doses tolerated by the ambulatory patient has little effect on recumbent hypertension [Not available on the commercial drug market Ed]

The ideal drug would dilate arterioles without other effects on the autonomic nervous system or on cardiac output This agent would have to have the unusual properties of reducing arteriolar smooth muscle tone without seriously affecting venomotor tone

SELECTED REFERENCES

Boura, A L, Green, A F, McCoubry, A, Laurence, D R, Moulton, R, and Rosenheim, M L Darenthin Hypotensive Agent of New Type, Lancet 2 17, 1959

Chapman, C B, and Gibbons, T B Diet and Hypertension A Review, Medicine 29 29, 1950

Dontas, A S, and Hoobler, S W Drug Treatment of Hypertension, Pharmacol Rev 5 135, 1953

[illegible] Activity [illegible] Hyper [illegible] k, 1959, [illegible]

Moyer, [illegible]

Page, I [illegible]

Paton, [illegible]

Pickering, G W High Blood Pressure, New York, 1955, Grune & Stratton

Schroeder H A Hypertensive Diseases Causes and Control, Philadelphia, 1953, Lea & Febiger

[illegible] 9 383 540 703 712, 839 1954 [illegible] Charles C Thomas, Publisher [illegible] ial Reference to Chlorothiazide,

*Table 27 Cerebral Hemodynamic Effect of Blood Pressure Elevation to Hypertensive Levels in Normal Subjects**

	Metaraminol		*Norepinephrine*	
	Control	*Drug*	*Control*	*Drug*
Mean Blood Pressure (mm Hg)	88	128	94	124
Cerebral Blood Flow (ml /100 Gm./min)	58	53	57	50
Cerebral Oxygen Uptake (ml /100 Gm /min)	3 4	3 2	3 7	3 5
Cerebrovascular Resistance (MBP/CBF)	1 6	2 4	1 7	2 6

*Average values in 11 patients
MBP = Mean blood pressure
CBF = Cerebral blood flow

is primarily that of peripheral vasoconstriction with minimal direct cardiac effect (Fig 10) Consequently, the primary response to an infusion of norepinephrine is a rise in diastolic blood pressure with an associated and secondary rise in systolic pressure (Figs 10 and 11)

Throughout the literature, pharmacodynamic studies have been done on normal subjects, and deductions thus have been drawn as to the probable action of these drugs in various disease states This has been particularly true of drugs which affect the cardiovascular and the autonomic nervous systems It has become increasingly obvious that such deductions are frequently inaccurate For example, when vasoconstrictor drugs are given to normotensive subjects and the blood pressure increased to hypertensive levels, blood flow through such vital areas as the brain and the kidneys is reduced Contrariwise, when the blood pressure is raised from shock levels to normotensive levels, blood flow, which was previously depressed in these areas, increases toward normal Similar discrepancies have been noted when electrocardiographic observations have been made during the administration of vasopressor agents to the normotensive subject (made hypertensive by the drug) as compared to the patient who was previously hypotensive and who was then made normotensive (rather than hypertensive) by the drug

Cerebral Hemodynamic Effects —When the blood pressure is increased from normotensive to hypertensive levels, cerebral blood flow is reduced slightly (Table 27) because of the vasoconstrictive effect of the drugs on the cerebral vessels Moreover, in the presence of hypotension due to shock or to ganglionic blockade (Table 28) the cerebral arterial pressure is inadequate to maintain blood flow through the brain and as a result, the cerebral blood flow is reduced also The brain partly compensates for the reduced cerebral blood flow by extracting more oxygen from that blood which is circulating through it However, when the mean cerebral arterial blood pressure is reduced below 55 mm Hg, cerebral blood flow may be reduced to a point at which the increased extraction of oxygen may not be adequate As a result, cerebral oxygen uptake is reduced and hypoxia results Apparently, there is very little difference in this cerebral hemodynamic response whether the hypotension is produced by hemorrhage or hypotensive drugs such as ganglionic blocking agents (Table 28) The degree of blood pressure reduction is the important feature since the cerebral blood flow during hypotension is en

cessive doses are used (Fig 11) Thus, when a continuous infu[illegible] is given, systolic blood pressure rises (due to the increase in card[illegible] whereas the diastolic blood pressure falls By contrast, the action of [illegible]

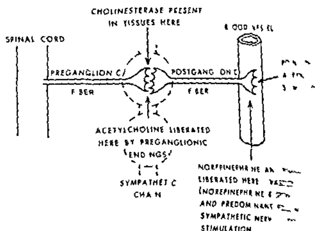


Fig 10 —Site of action of vasoconstrictor agents Not all [illegible] are equally responsive to the sympathomimetic agents It is [illegible] have a predominant constrictive effect in less vital vascular be[illegible] strictive effect in such vital areas as the brain, heart liver and k[illegible]

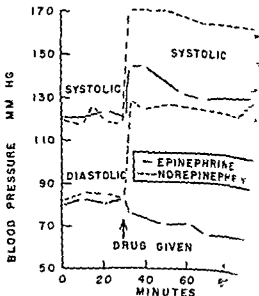


Fig 11 The blood pressure response to norep[illegible] The systolic pressure rises after both but after epineph[illegible] a result of an over all reduction in peripheral resistance and Mills L C Norepinephrine Effect in Normal [illegible] Unresponsive to Other Measures Am J Med 15 33



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*Table 29 Observations on Cerebral Oxygen Metabolism and Cerebral Hemodynamic Response to Blood Pressure Elevation With Vasopressor Agents Following Initial Hypotension Due to Ganglionic Blockade or Shock**

Patient	Ganglionic Blocking Agent	Vasopressor Agent	Mean Blood Pressure (mm Hg)			Cerebral Blood Flow			Cerebrovascular Resistance			Cerebral O_2 Consumption		
			C	D	V	C	D	V	C	D	V	C	D	V
	Patients Who Were Hypotensive Due to Ganglionic Blockade													
1	Arfonad	Nor epinephrine	96	52	120	40	25	36	24	21	33	26	20	24
2†	Arfonad	Nor-epinephrine	96	75	105	58	38	51	17	20	21	28	29	32
3	Arfonad	Nor-epinephrine	110	58	110	48	35	38	23	17	29	25	27	29
4	Arfonad	Nor-epinephrine	94	44	110	41	25	35	23	18	31	29	26	26
5	Hexamethonium	Aramine	108	61	120	52	44	56	21	14	21	41	37	38
6	Hexamethonium	Aramine	98	68	118	49	36	64	20	19	18	26	22	29
7	Hexamethonium	Aramine	104	61	105	75	36	65	14	17	16	41	33	40
8	Hexamethonium	Nor epinephrine	100	80	140	69	58	65	15	14	22	30	26	34
9	Hexamethonium	Nor epinephrine	96	54	118	56	40	50	17	14	24	28	31	25
10	Hexamethonium	Nor epinephrine	100	53	96	54	34	42	19	16	23	36	29	30
11‡	Pend omide	Nor epinephrine	111	66	110	49	51	53	23	12	21	29	32	30
Mean			101	61	114	54	38	50	20	17	24	31	28	31
	Patients Who Were Hypotensive Due to Shock													
	ETIOLOGY		S		V	S		V	S		V	S		V
12	Hemorrhage	Nor epinephrine	52		94	42		56	12		17	20		34
13	Cardiogenic	Nor epinephrine	48		100	38		48	13		21	23		30
14	Septicemia	Nor epinephrine	40		95	32		40	13		24	18		24

*From Moyer, J H, and Morris, G Cerebral Hemodynamics During Controlled Hypotension Induced by the Continuous Infusion of Ganglionic Blocking Agents (Hexamethonium Pendiomide, and Arfonad) J Clin Invest 33 1081, 1954

†When blood pressure increased from 105 to 145, the cerebral blood flow decreased to 38

‡When blood pressure increased from 110 to 155, the cerebral blood flow decreased to 49

C = Control observations D = observations after blood pressure reduction with ganglionic blocking agent V = observations after blood pressure elevation with vasopressor agent S = observations while in shock

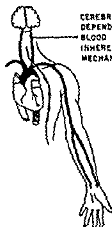
*Table 28 Cerebral Hemodynamic Effect of Blood Pressure Reduction**

Cause of Blood Pressure Reduction	Hexamethonium		Trimethaphan		Shock			
					Hemorrhage		Cardiogenic	
Function Study	Control	Drug	Control	Drug	Recovery†	Shock	Recovery†	Shock
Mean Blood Pressure (mm Hg)	99	69	99	57	105	59	112	58
Cerebral Blood Flow (ml /100 Gm /min	57	42	52	36	54	32	49	36
Cerebral Oxygen Uptake (ml /100 Gm /min)	3 2	2 9	3 1	2 8	3 0	2 1	3 1	2 4
Cerebrovascular Resistance (MBP/CBF	1 8	1 5	2 0	1 7	2 0	1 6	2 3	1 6

*Average values for 6 or more patients
†One to two weeks after recovery

tirely dependent on the cerebral arterial blood pressure and the inherent cerebrovascular vasoregulatory mechanisms Fig 12) The degree of cerebral vasoconstriction is unrelated to sympathetic nervous system activity in man

When the blood pressure is raised from hypotensive toward normotensive levels cerebral blood flow (which was reduced because of the hypotension) increases significantly and it may return entirely to normal Table 29 and Fig 13) Table 29 summarizes some observations that we have made on cerebral hemodynamics before and after the administration of vasopressor agents to patients who were hypotensive either from hemorrhage or following the administration of ganglionic blocking agents It is quite obvious that when the cerebral blood flow was depressed due to hypotension this was followed by a significant increase in





response has been observed with norepinephrine, metaraminol (Aramine), and phenylephrine (Neo Synephrine) We have not had occasion to study the response to other vasopressor agents when administered to patients in shock The increase in glomerular filtration rate can be observed clinically by observing the increase in urine output Generally, when the urine output is adequate, the blood pressure is adequate to maintain renal blood flow as well as blood flow through the other vital areas

Table 30 Renal Hemodynamic Response to a Continuous Infusion of Various Vasopressor Agents in Normal Human Subjects

	Mean Arterial Blood Pressure (Mm Hg)			*Glomerular Filtration Rate (Ml/Min)*			*Renal Blood Flow (Ml/Min)*			*Renal Vascular Resistance (MBP/RBF)*		
Drug	*Control*	*Drug*	*Per Cent of Control*	*Control*	*Drug*	*Per Cent of Control*	*Control*	*Drug*	*Per Cent of Control*	*Control*	*Drug*	*Per Cent of Control*
Methoxamine	90	122	136	115	75	63	1129	668	59	0 082	0 445	615
Norepinephrine	97	132	136	108	102	94	1143	705	63	0 091	0 195	224
Metaraminol	86	125	147	99	109	109	1134	1038	94	0 082	0 128	162

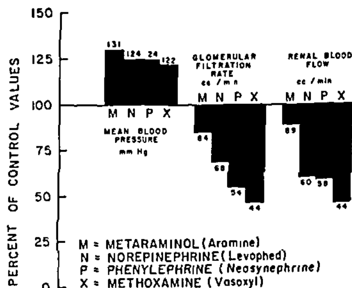
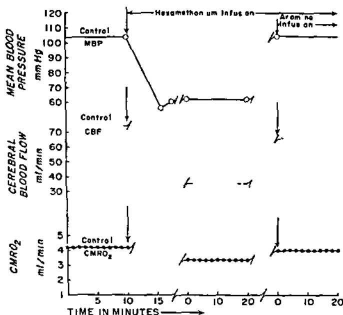


Fig 14 —A comparison of the renal vasoconstriction produced by various vasopressor agents in the normal dog

In patients who have suffered severe hemorrhage and are markedly hypovolemic, *renal function will not improve* to the same extent that it will in the patient who is hypotensive but normovolemic, as, for example, in the patient who is hypotensive and oliguric following a hypotensive drug It has also been shown experimentally in dogs that are *in severe shock* due to hemorrhage that administration of norepinephrine results in no improvement in renal blood flow and may

cerebral blood flow when the patient was again made normotensive, although frequently it did not return entirely to normal

In patients with severe hypertensive vascular disease, the degree of reduction in cerebral blood flow due to hypotension is even more marked at equivalent levels (hypotensive) of absolute blood pressure than it is in patients who were previously normotensive Consequently, when shock is being treated in patients who previously had severe hypertensive vascular disease, it is necessary to increase the arterial blood pressure to mildly hypertensive levels if the cerebral blood flow is to be returned to normal



Renal Hemodynamic Responses—In some respects the renal hemodynamic responses to vasopressor agents are quite similar to those observed in the brain When a vasopressor agent is administered to a normotensive dog (Fig 14) or to a normotensive human subject (Table 30), renal blood flow decreases There is considerable variation in this response among the different vasopressor agents Methoxamine (Vasoxyl) has the most marked renal vasoconstrictive effect (Fig 14 and Table 30) when administered to the normal subject

By comparison with the normal subject, when vasopressor agents are administered to patients whose renal function is depressed due to hypotension, glomerular filtration rate and renal blood flow increase This occurs whether the hypotension be due to drug administration, hemorrhage, or shock from other causes A similar

Figs 17*A* and 17*B* summarize the responses of two patients who were in shoc but in whom the blood volume was normal Patient J M (Fig 17*A*) had seve hypopotassemia (2 2 mEq per liter) associated with leukemia Glomerular filtr tion rate and renal blood flow increased to approximately two thirds of the norm value when the blood pressure was increased with norepinephrine Subsequentl the cause of the hypotension was determined and potassium was administered t this patient, following which renal function returned entirely to normal Nonethe less the vasopressor agent had proved lifesaving by preventing cerebral ischemi and irreversible damage to the brain and other vital tissues while laboratory pro cedures were being carried out in order to establish the correct diagnosis, whic fortunately was amenable to specific therapy

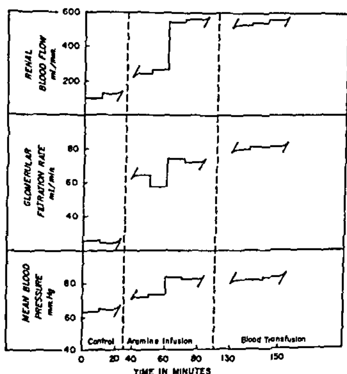


Fig 15*B* —A response similar to that shown in Fig 15*A* was observed when metaraminol was administered to a similar patient (From Moyer, J H, Morris, G, and Beazley H Renal Hemodynamic Response to Vasopressor Agents in the Treatment of Shock, Circulation 12 96 107, 1955 reprinted by permission)

Patient D L (Fig 17*B*) was oliguric due to hypotension resulting from a myocardial infarction When the hypotension was corrected, glomerular filtration rate and renal blood flow increased When the norepinephrine was temporarily discontinued, renal function decreased Subsequently, the condition of the patient improved so that norepinephrine was no longer required to maintain the blood pres sure, and renal function remained stabilized

Even in the presence of renal damage, when function is further impaired by hypotension vasopressor agents may improve renal function Patient L H (Figs

actually decrease it Likewise, the normovolemic patient who is in shock and has deteriorated, thus requiring large doses of vasopressor agents to maintain blood pressure, will not obtain a response comparable to the patient who is less ill This is particularly true in patients who are in the terminal stages of cardiogenic shock or hypotension from an overwhelming infection

F

given

(Fig

were in hemorrhagic shock, produced a rather dramatic increase in glomerular

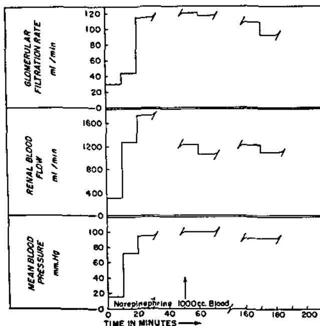


Fig 15*A*—Renal hemodynam c r
a patient who was in shock due to blood
filtration rate and renal blood flow incr
H Renal Hemodynamic Response to
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filtration rate and renal blood flow Although these determinations were not accurate during the period of maximum hypotension (due to the low urine output), it is obvious that there was a progressive rise in renal function as the blood pressure was returned to normotensive levels Oddly enough, renal function during the infusion of norepinephrine was approximately the same as it was following blood replacement therapy

Fig 16 compares the renal hemodynamic response to norepinephrine and metaraminol in the same patient If any difference does exist, metaraminol produces a slightly greater improvement in renal function than norepinephrine at equivalent blood pressure levels

is observed When the vagus is blocked with atropine, the vagal response is entirely lost and tachycardia follows (Figs 20*A* and 20*B*) This reflex vagal response to hypertension resulting from vasopressor administration also tends to produce arrhythmias Therefore it is essential that the blood pressure not be increased to hypertensive levels, particularly in the presence of myocardial disease, otherwise

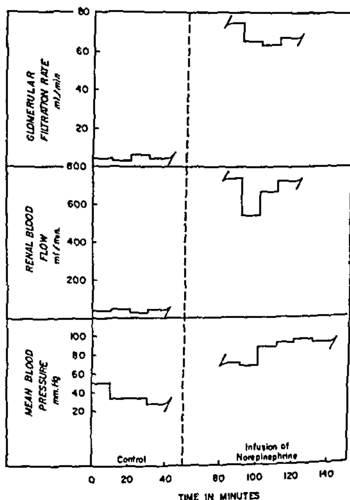


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disastrous results may follow Also, it is probably not wise to administer cholinergic blocking agents such as atropine during vasopressor administration since the vagal restraining effect on blood pressure is then lost and the blood pressure may become quite labile and difficult to regulate Likewise the tachycardia may become quite severe

When the blood pressure is raised from hypotensive levels to normotensive

18*A* and 18*B*) had severe renal damage following intravaginal administration of Lysol in an attempt at self-induced abortion She became oliguric but not anuric On the third hospital day she developed shock and became nearly anuric, at which time the initial renal function tests were done Following the administration of norepinephrine, renal function, including the excretion rates of water and electrolytes, increased to the preshock levels Although these values cannot be considered as absolute, due to the limitations of the techniques under these circumstances, they do give some estimate of qualitative directional changes indicating some improvement in renal function

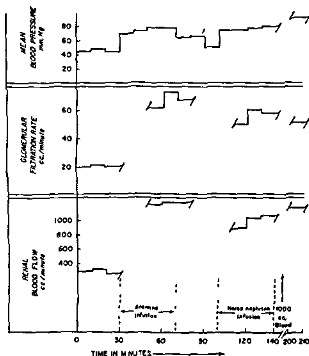


Fig 16 —Comparison of the renal hemodynamic response to metaraminol and norepinephrine in the same patient As the blood pressure was returned to normal, glomerular filtration rate and renal blood flow increased There was very little difference in response to the two drugs (From Moyer, J H, and Beazley H L Effectiveness of Aramine in the Treatment of Shock, Am Heart J 50 136, 1955)

When blood pressure reduction is excessive following the administration of hypotensive agents, patients may become anuric due to inadequate glomerular perfusion pressure Under these circumstances, vasopressor agents produce an immediate return of glomerular filtration rate and urine volume toward normal (Figs 19*A* and 19*B*)

Cardiac Effects of Vasopressor Agents —

Arrhythmias —When the blood pressure is raised from normotensive to hypertensive levels with vasopressor agents, bradycardia due to reflex vagal effects

PERIPHERAL RESISTANCE —Calculated peripheral resistance usually increa but this is not always the case When the blood pressure is returned to nor with vasopressor agents, cardiac output increases The administration of n epinephrine is associated with an increase in peripheral resistance Thus, vasop sor agents are capable of *increasing vasoconstriction over and above that wh* has resulted from increased sympathetic nervous system activity resulting from hemorrhage It should be noted, however, that in hemorrhagic shock cardiac o put increases considerably more after blood transfusions than it does during the ministration of vasopressor agents

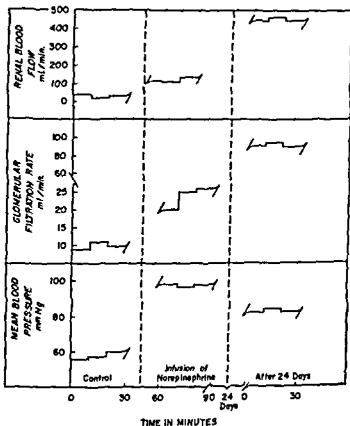


Fig 18A —Patient (L H) in shock with primary renal damage due to Lysol Glomer lar filtration rate and renal blood flow were markedly depressed As the vasopressor age was administered both glomerular filtration rate and renal blood flow increased The i crease in renal blood flow may well have prevented the development of irreversible ren damage in this instance (From Moyer J H, Morris C, and Beazley, H Renal Hem dynamic Response to Vasopressor Agents in the Treatment of Shock, Circulation 12 96 10 1955 reprinted by permission)

EFFECTS ON PULMONARY CIRCULATION —Vasopressor agents also constrict th pulmonary vessels, resulting in a marked increase in pulmonary artery pressure This could be a reflection of increased venous return and inadequate pulmonar outflow associated with the bradycardia, rather than a direct effect of the drug or

ones, reflex arrhythmias rarely, if ever, occur When the cardiovascular system of patients has deteriorated and it becomes necessary to administer excessive doses of norepinephrine, toxicity may occur and arrhythmias may be produced Such reactions are occasionally observed in patients with overwhelming infections and following massive myocardial infarctions

Cardiac Output—When the blood pressure is raised from normotensive to hypertensive levels, norepinephrine produces little, if any, increase in cardiac output Metaraminol likewise does not alter cardiac output When atropine is given during the administration of norepinephrine or metaraminol, there is frequently a sharp increase in cardiac output and in pulse rate This does not necessarily mean that the vasopressor agent affects the heart directly, more likely it produces venous and capillary constriction which causes an increased venous return These effects followed by the vagal release due to the atropine, result in an increase in pulse rate and in cardiac output

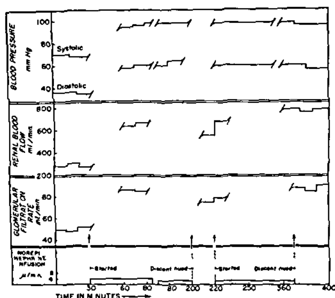


Fig 17B—Renal hemodynamic response to norepinephrine in a patient with normovolemic shock of moderate severity due to a myocardial infarction (Patient D I) (From Moyer J H, Morris, G, and Beazley H Renal Hemodynamic Response to Vasopressor Agents in the Treatment of Shock Circulation 12 96 107, 1955 reprinted by permission)

Probably one of the major factors responsible for improved peripheral circulation following the increase in blood pressure from shock levels to normotensive ones during the administration of vasopressor agents is the increased venous return which is followed by an increase in cardiac output This response can occur without a direct effect of the drugs on the heart although some of the agents may have a direct cardiac stimulant effect Following hemorrhage or cardiogenic shock, cardiac output is depressed

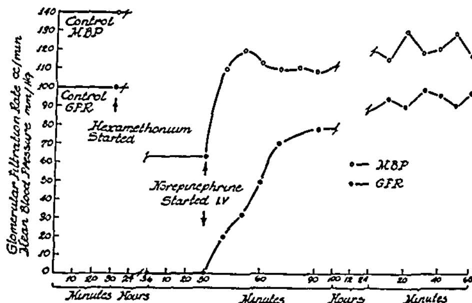


Fig 19A —Renal response to blood pressure elevation with norepinephrine in a patient who became anuric following an excessive response to hexamethonium (From Moyer, J H, and Dennis, Edward W Treatment of Hypertension Part IV Pharmacology and Therapy of Hypertensive Emergencies, South M J 49 580, 1956)

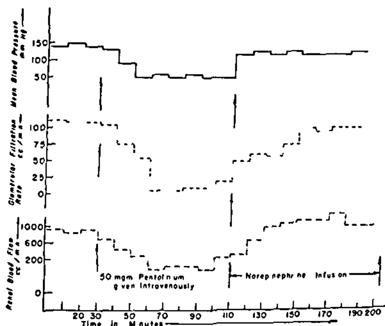


Fig 19B —Renal response to norepinephrine in a patient who became markedly hypotensive following the administration of pentolinium (From Moyer, J H, and Dennis, Edward W Treatment of Hypertension Part IV Pharmacology and Therapy of Hypertensive Emergencies, South M J 49 580, 1956)

subsequent increase in pulse rate the pulmonary hypertension persists suggesting a direct constrictor effect of the drug on the pulmonary vessels

THE DRUGS OF CHOICE

Numerous vasopressor agents are available for clinical use Generally speaking, the clinician should select a short acting drug for continuous intravenous infusion The outstanding agent in this category is norepinephrine (levarterenol, Levophed) In addition, the therapist should select a longer acting vasopressor

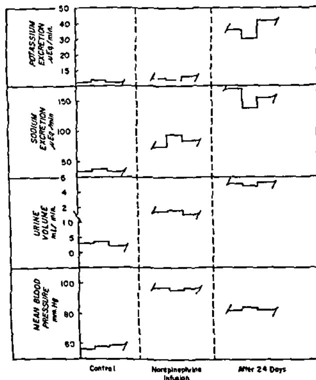
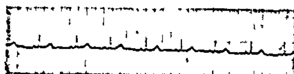


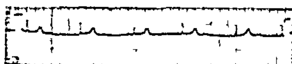
Fig 18B —Despite a persistent depression of glomerular filtration rate in the presence

mission)

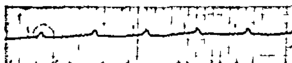
agent which is suitable for continuous intravenous infusion as well as for intermittent intramuscular use In this category I prefer metaraminol (Aramine) and phenylephrine (Neo Synephrine) Some therapeutists prefer methoxamine (Vasoxyl) because it is somewhat longer acting than phenylephrine and metaraminol Having selected one or two of these agents, it is best to use them more or less exclusively This allows the therapeutist to become familiar with the characteristics



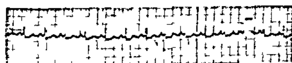
A Lead aVf - Control
Blood Pressure 122/81
Heart Rate 71



B Lead aVf - Methoxamine 188 γ /Kg/min
Blood Pressure 165/97
Heart Rate 47



C Lead aVf - Methoxamine 188 γ /Kg/min
(Immediately before administration of atropine)
Blood Pressure 175/100
Heart Rate 47



D Lead aVf - 5 minutes after atropine 1 mgm IV
Blood Pressure 191/120
Heart Rate 128

Fig 20B—Electrocardiographic changes during the intravenous infusion of methoxamine (From Mills, L C, and Moyer, J H Methoxamine Effect on Blood Pressure and Renal Hemodynamics, Am J M Sc 233 409, 1957)

of the vasopressor agent that he employs When the therapeutist employs a la variety of compounds, it is difficult to evaluate the desirable qualities as well as undesirable ones for each drug Occasionally a patient may become unresponsi to one of the vasopressor agents but may respond to another When this occu however, the patient s general condition is rapidly deteriorating and the prognos is usually hopeless

The pharmacodynamics of metaraminol are almost identical with phenyl ephrine, although it apparently produces somewhat less renal vasoconstriction anc is not quite as potent Mephentermine (Wyamine) is of little value since it is unpredictable and not adequately potent Methoxamine (Vasoxyl) may be as

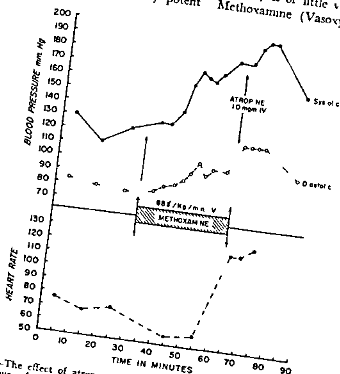


Fig 20A —The effect of atropine administration on blood pressure and pulse rate during the intravenous infusion of methoxamine (From Mills L C and Moyer J H Methoxamine Effect on Blood Pressure and Renal Hemodynamics Am J M Sc 233 409 1957)

good as phenylephrine, but since it produces more pulmonary and renal vasocon striction than do norepinephrine, phenylephrine and metaraminol, as well as some other undesirable effects when used for the treatment of shock, it should be used s an alternative drug for intermittent intravenous or intramuscular administra on in those patients who do not respond to phenylephrine or metaraminol How er methoxamine is effective in preventing a decrease in blood pressure when used ophylactically for the prevention of hypotension during spinal anesthesia and hen used for this purpose it has the advantage of longer duration of action with t central nervous system stimulation

countered with extravasation of phenylephrine and metaraminol Epinephrine is contraindicated as a vasopressor agent for the treatment of shock Metaraminol and phenylephrine can be administered by intermittent intramuscular or subcutaneous injections, but the degree of blood pressure response following this method of administration is unpredictable The drugs are administered by this route in emergency conditions when a continuous intravenous infusion is not possible at the moment

Hypotension and Shock Due to Severe Infections—The prognosis is poor in patients who require vasopressor agents because of hypotension due to infection This merely emphasizes that unless the etiology of the infection can be treated irrespective of the cause the patient in shock will ultimately succumb Therefore it is essential that the infection be treated vigorously with appropriate antibiotics and other means available for reducing toxemia The patients should be well hydrated but not overhydrated When the infectious process appears to be toxic and temporarily unresponsive to antibiotic therapy, steroids should be administered in the amount of 100 to 200 mg of hydrocortisone every 8 hours

Vasopressor agents are only temporary expedients and the patients frequently respond poorly to them since the toxic process is associated with widespread vascular damage as well as the loss of intravascular fluids Since potency is usually an important factor, we consider norepinephrine to be the agent of choice here However Weil has found metaraminol (Aramine) effective under these circumstances Ezzo found norepinephrine superior to methoxamine in the treatment of bacterial shock Uhl reported a case of shock from meningococcemia that failed to respond to all forms of treatment including adrenocortical therapy but that responded to norepinephrine with ultimate recovery

Hypotension Associated With Drug Administration—In the treatment of hypotension due to drug administration, the prognosis is usually good when the hypotension is due to vasodilatation rather than a toxic effect on the myocardium or severe arrhythmia such as ventricular fibrillation Frequently the vasoconstrictor response is only required for short periods A frequent use of vasopressor agents is to combat excessive hypotension associated with antihypertensive agents particularly the ganglionic blocking agents Vasopressor agents are also useful for the treatment of hypotension associated with overdoses of barbiturates

When the hypotension is not severe, a single intravenous injection of phenylephrine (4 to 10 mg) or metaraminol (5 to 10 mg) will be adequate This can be followed by the intramuscular or subcutaneous administration of the effective dose of metaraminol or phenylephrine every 20 to 40 minutes or as frequently as necessary

When the hypotension is more persistent, it is usually best to give a vasopressor drug by continuous intravenous infusion Phenylephrine and metaraminol are easier to manage and less variable but may not be sufficiently potent If not then norepinephrine should be used starting with a concentration of 4 mg per 1 000 ml of intravenous fluid and increasing the concentration as much as needed

Surgical Hypotension—Generally speaking when shock occurs in the surgical patient it is a direct result of some complicating factor It goes without saying that the primary objective should be to correct the complicating disturbance

CLINICAL USE

Cardiogenic Shock Vasopressor agents are useful in numerous circumstances when the blood pressure is not high enough Probably the most frequent indication for these compounds is hypotension due to cardiac disease, i e, cardiogenic shock This is seen most frequently following myocardial infarctions and less frequently in association with severe heart failure and following pulmonary infarction Results indicate that shock resulting from a cardiac origin has a poor prognosis, and a high percentage of these patients die even though the blood pressure is returned toward normal with vasopressor agents However, almost all investigators of this problem feel that many of the patients who do survive most surely would have died had not vasopressors been used in the acute episode, and a survival rate greater than 50 per cent has been reported by some investigators Siglin reported a case of myocardial infarction with survival following use of norepinephrine intravenously for 14 days

Details of Regimen —Particular care should be exercised to avoid sudden and excessive increases in blood pressure in the presence of cardiovascular disease particularly in patients with myocardial infarctions In a patient who was previously normotensive it is usually preferable to maintain the systolic blood pressure within the range of 90 to 110 mm Hg When the blood pressure is allowed to increase to hypertensive levels untoward effects may occur As noted above any of the vasopressor agents may produce arrhythmias when the blood pressure is allowed to increase to hypertensive levels ventricular fibrillation and death may follow When the blood pressure is allowed to increase excessively in patients with heart failure and poor myocardial function acute pulmonary edema may be precipitated This is particularly likely to result when large amounts of fluid are given concurrently

It should also be noted that the sudden administration of 200 to 300 ml of 5 per cent glucose or normal saline may precipitate or aggravate pulmonary edema in a patient who is already in heart failure When the patient is anuric and the administration of fluids contraindicated then vasopressor agents such as metaraminol or phenylephrine can be given intramuscularly or subcutaneously every 20 minutes to 2 hours thus avoiding the administration of fluids Irrespective of the route of drug administration it is a good rule to maintain the blood pressure at the minimum level that will maintain the circulation so that the patient is free of clinical manifestations of shock This assures adequate blood supply to vital tissues and at the same time keeps the cardiac work load at the minimum level necessary for life When the patient has had severe or malignant hypertension prior to the emergency it is frequently necessary to keep the blood pressure at mildly hypertensive levels in order to ensure an adequate blood flow to the brain

Close nursing supervision is required when intravenous infusions of vasopressor agents are being used Intravenous infusions of norepinephrine are preferable for severe shock However, when less potent agents are required, phenylephrine (Neo Synephrine) or metaraminol (Aramine) may be preferable, especially when prolonged administration is required After the infusion rate has been regulated and the blood pressure stabilized with these longer acting agents, fluctuations in blood pressure are less likely to occur In addition, cutaneous sloughs are not en

to be as effective as methoxamine, with the latter having the longer duration of action Complications were minimal with both drugs It appears that both of these agents are equally effective when used to prevent hypotension from spinal anesthesia, and the drug of choice in this instance would depend on the clinician's *familiarity with one or the other drug*

THE ADMINISTRATION OF VASOPRESSOR AGENTS

Norepinephrine—Norepinephrine must be given by continuous intravenous infusion and the dose must be individually titrated for each patient i e, the rate of infusion is adjusted so as to maintain the blood pressure at low normotensive ranges (systolic pressure between 90 and 110 mm Hg) When norepinephrine is used, the concentration of this agent in the infusion solution is 4 mg per 1,000 ml of 5 per cent glucose or normal saline When the patient is in congestive failure *saline should be avoided When the required rate of infusion becomes too great* at this concentration, the concentration of norepinephrine is increased in 4 mg increments per 1,000 ml of solution until the required response is obtained There is no limit to the concentration of norepinephrine that may be employed, concentrations as great as 48 mg per 1 000 ml of solution have been used safely However when increasing concentrations are required, the prognosis is usually poor and rarely do patients recover when more than 12 mg per liter of fluid is required *to maintain the blood pressure In patients with cardiogenic* shock due to myocardial infarction, it is particularly important that the blood pressure not be increased above normotensive ranges, or disastrous results may follow Therefore it is very important that constant supervision be given to the intravenous administration of vasopressor agents Extreme caution must be used at all times in order to avoid extravasation *of the infusion, else serious cutaneous sloughs will occur*

When norepinephrine is to be administered for a prolonged period of time it is necessary that an intravenous catheter be used This is done either by exposing a vein and inserting a plastic tube into it or by using a relatively large (16 gauge) needle through which the plastic catheter is inserted into the vein When a "cut down" is used and the vein ligated at the site of insertion of the catheter, it is necessary to insert the catheter far enough so that the tip lies in a relatively large *vein where the flow of blood is quite large* If these precautions are not followed during prolonged infusion of norepinephrine, a cutaneous slough will frequently be produced This no doubt results from back diffusion of the drug into smaller vascular channels, which is followed by intense vasoconstriction and focal ischemia followed by necrosis In my experience, it has usually been best to insert a plastic catheter *through a needle into the femoral vein and up into the* inferior vena cava When a 'cut down' is required, it is best to use the saphenous vein in the groin inserting the plastic catheter up into the inferior vena cava *Foot veins should be avoided whenever possible*

Long-Acting Vasopressor Agents—Of the longer acting vasopressor agents for continuous intravenous infusion, phenylephrine (*Neo Synephrine*) and metaraminol (Aramine) seem to be the agents of choice The longer action of *metaraminol* according to Weil and Spink also offers a distinct advantage over norepinephrine in that the route of administration may be changed to intermit

However, it may become necessary to support the blood pressure until specific corrective measures can be instituted. Even when due to hemorrhage and other surgical etiologies, vasopressor agents alone or together with blood may prove to be valuable as a temporary expedient for maintaining blood pressure in those patients who do not respond promptly and adequately to blood and fluid administration.

When surgical shock has existed for prolonged periods, it may not respond to fluid replacement therapy and corrective surgery. This has been well documented experimentally in animals in which shock following blood loss became irreversible after prolonged periods of time, despite transfusion of more blood than was originally removed. Under these circumstances, further fluid administration also will be valueless and is contraindicated since it may lead to acute heart failure and pulmonary edema. Undoubtedly, a large factor in the production of the so called "irreversible shock state" is damage to the brain and other vital organs as a result of inadequate perfusion pressure during the period of hypotension. It is inescapable that the sooner the blood pressure returns to a level adequate for perfusion of these vital organs, the more likely the patient is to recover, provided he does not die from the primary disease process which is responsible for the hypotension.

Hypotension during the postoperative period may also result from infection as a complicating factor. When this occurs, the hypotension should be treated as in any other instance of severe infection. The primary objective is to treat the infection.

TRAUMA.—Trauma is of extreme importance in the etiology of shock. Frequently these patients will not respond to blood and fluid replacement. It then becomes necessary to support the blood pressure with vasopressor agents. Patients with trauma to the brain are particularly likely to develop shock.

ISCHEMIA.—Ischemia during vascular surgery may be followed by severe hypotension, especially following surgery on major vessels such as the aorta and its branches. When the blood pressure is supported following release of the vascular clamps, excessive hypotension may be avoided. This is of importance since extreme blood pressure reduction for only 3 to 5 minutes may result in irreversible cerebral damage. It may become necessary to use an intra arterial infusion of a vasopressor agent. Probably phenylephrine is the agent of choice for this purpose, in a concentration of 15 to 20 mg per 1 000 ml of solution. If this is inadequate, then norepinephrine in a concentration of 2 mg per 1,000 ml of fluid may be employed.

SPINAL ANESTHESIA.—Vasopressor drugs have been extremely useful in preventing the blood pressure reduction which commonly results from spinal anesthesia. It has become the routine of many anesthesiologists to give one of these agents as a prophylatic measure. The longer acting vasopressor agents such as metaraminol (Aramine) and methoxamine (Vasoxyl) are more suitable for this purpose because of the longer duration of action as well as the ease of administration. A 10 mg dose of methoxamine is usually injected subcutaneously prior to induction of spinal anesthesia. The dose of metaraminol used by Poe was 3 to 5 mg. King and Dripps found that methoxamine was longer acting and that it offered other advantages over the other vasopressor agents. Poe found metaraminol

Mills, L C, and Moyer J H [illegible] dynamics, Am [illegible]

Mills, L C, and Moyer, [illegible] ous Vasopressor [illegible]

Mills, L C, Moyer, J [illegible], J M The Effect of Norepinephrine and Epinephrine on Renal Hemodynamics, Am J M Sc 226 653, 1953

Moyer, J H, and Beazley, H Effectiveness of Aramine in the Treatment of Shock, Am Heart J 50 136 1955

Moyer, J H Handley, C, and Huggins, R The Effect of Adrenergic Blockade and Norepinephrine on Renal and Cardiovascular Hemodynamics Following Hemorrhage Circulation Res 2 441, 1954

Moyer, J H, Morris, G, and Beazley, H Renal Hemodynamic Response to Vasopressor Agents in the Treatment of Shock Circulation 12 96, 1955

Moyer, J H, Morris, G, and Snyder, H A Comparison of the Cerebral Hemodynamic Response to [illegible] Subject, C [illegible]

Poe, M F The L [illegible] 15 517, 1 [illegible]

Sampson, J J, and Zipser, A Norepinephrine in Shock Following Myocardial Infarction Influence Upon Survival Rate and Renal Function Circulation 9 38, 1954

Selzer A, and Rytand D A Use of Drugs in Shock Accompanying Myocardial Infarction J A M A 168 762, 1958

Siglin I S Prolonged Use of Arterenol for Shock Following Myocardial Infarction With Patient Survival, A M A Arch Int Med 98 372, 1956

Weil M H, and Spink W W Clinical Studies on a Vasopressor Agent Metaraminol (Aramine) I Observation in Normotensive Subjects, Am J M Sc 229 661, 1955

tent subcutaneous or intramuscular injection (every ½ hour to 2 hou circumventing some of the problems of continuous nursing care as wel sibility of cutaneous sloughs The initial concentration of phenylephi metaraminol is 25 mg per liter of 5 per cent glucose or normal saline centration is inadequate then it should be increased in increments of 25 an adequate response is obtained without excessive fluid administration these agents are given by intravenous infusion the duration of action is con shorter than when an equally effective vasopressor dose is given subcutane

Of the drugs available for subcutaneous or intramuscular adminis phenylephrine and metaraminol seem to be quite adequate in most instances clinicians prefer methoxamine (Vasoxyl) The usual initial dose of phenylep is 4 or 5 mg given intramuscularly and if this is not adequate it can be incre in 5 mg increments repeated every 10 to 20 minutes as required to maintain blood pressure The initial intramuscular dose of metaraminol is 3 to 5 mg W this is inadequate the dose can be increased in 3 to 5 mg increments and repea as frequently as every 10 to 20 minutes

Combinations.—It is frequently advantageous to use a combination of pheny ephrine and norepinephrine in the same infusion This gives the therapist the potency of norepinephrine with less fluctuation in blood pressure as a result of the phenylephrine in the solution In addition, the vasopressor effect is not lost as rapidly and an occasional patient obtains an effective vasopressor response to this combination whereas an excessive dose of norepinephrine or phenylephrine would have been required had the agents been administered alone

EVALUATION OF NEW VASOPRESSOR AGENTS

A vasopressor agent which is superior to those already available should increase the blood pressure promptly and should maintain or show an increase in blood flow to vital areas at the expense of less essential vascular beds such as the skin and striated muscles In other words it should increase over all peripheral resist ance but at the same time increase the blood flow through the coronary the renal the hepatic and the cerebral vessels The drug should have minimal side effects and should maintain or increase cardiac output It should not produce cardiac arrythmias The degree of vasoconstriction produced by vasopressor agents should be controlled readily tachyphylaxis and secondary vasodilation following discon tinuation of the drug should not occur The drug should be effective when ad ministered by different routes Especially it should not be necessary to give large volumes of fluid when the drug is administered by the intravenous route Local tissue damage at the site of injection should not occur following any route of ad ministration

SELECTED REFERENCES

zo J A and Knight W Bacterial Shock A M A Arch Int Med 99 701 1957

oe B D and Dripps R D The Use of Methoxamine for Maintenance of the Circula tion During Spinal Anesthesia Surg Gynec & Obst 90 659 1950

rty W Moyer J and Chapman D The Cardiovascular and Renal Hem Effects of Aramine Am. Heart J 47 745 1954

lowing sympathectomy which proved to be inadequate, and in vascular diseases involving both upper extremities where surgery, of necessity, is more extensive and apt to be ineffective

Before a vasodilator drug is employed for prolonged periods, the therapist should ascertain the inoperability of the condition For example, if the obstruction to the circulation is a localized process, arterial homograft or arterial bypass is the therapy of choice Contrariwise, the latter approach is of little value when the disease is a diffuse process

The effective medical management of occlusive vascular disease is largely dependent upon factors other than vasodilator agents, which, if ignored, usually render the drugs ineffective There are frequently one or more ancillary disease processes which result in increased disparity between blood supply and demand i e congestive heart failure, anemia, diabetes, and recent arterial occlusion The frequency with which occlusive manifestations diminish or even disappear following resolution of such ancillary factors is remarkable The importance of these associated conditions is re emphasized in respect to their role in the production of gangrene Somewhat in excess of 50 per cent of extremities which are amputated are lost as a result of trauma or infection, both of which will be greatly magnified in the event the patient's condition is not optimum A thorough orientation of the patient regarding such matters as foot care, avoidance of temperature extremes tobacco exercise, etc with reassurance, is usually a simple matter and is invariably expedient and limb preserving

Evaluation of Results—In estimating a patient's response to vasodilator therapy the physician should remind himself that symptoms of occlusive arterial disease are not always stable and spontaneous improvement shortly after the onset of the complaint is frequently observed Variations in the degree of exercise tolerance are a part of the natural history of the disease Often the therapeutist must be satisfied with symptomatic relief alone, with the use of vasodilators Similarly surgery may produce gratifying healing of ulcerations and warmth in a previously cold extremity but no change in exercise tolerance

Dangers—Finally, the use of vasodilating drugs is not without risk, and such undesirable complications as activation of quiescent peptic ulcers coronary thrombosis, myocardial infarction, and cerebral thrombosis do occur The possibility of secondary arterial and venous thrombosis has already been mentioned Side effects from the drugs vary and may occasionally be so numerous or so unpleasant as to prevent continued use

PHARMACOLOGIC CONSIDERATIONS

Vasodilator drugs act either directly on the smooth muscle of the arterioles or indirectly by depressing the number of vasoconstrictor impulses traveling over the sympathetic nervous system, i e, by decreasing the degree of functional constriction of the arterioles Most of the effective therapeutic agents in use today act by the latter mechanism, i e, depressing the sympathetic nervous system Obviously the impedance to the circulation must be due in part to vasoconstrictive nervous impulses if the drugs blocking these impulses are to be effective

The drugs which are effective in depressing the sympathetic nervous system

THE CHOICE OF VASODILATOR DRUGS FOR THE TREATMENT OF PERIPHERAL VASCULAR DISTURBANCES

John H Moyer, M D, and
Charles H Heider, M D

INTRODUCTION

Vasodilator drugs have been advocated enthusiastically from time to time for the treatment of peripheral vascular disease Although initial reports for any one drug have usually been favorable, subsequent reports by other investigators have been less encouraging To date there is no single effective measure for the treatment of occlusive disease which has gained wide acceptance The major difficulty encountered in the systemic administration of vasodilator drugs is their inability to produce selective vasodilation in specific ischemic areas without simultaneous generalized vasodilation This may result, paradoxically in a reduction of blood flow to the area of vascular disease particularly when drugs which reduce systemic blood pressure are used in treating morphologic occlusive disease In fact hypotension has been implicated in the occurrence of secondary arterial and venous thrombosis in such a situation This hazard seems particularly imminent in cases of unilateral occlusive disease in which generalized vasodilation would logically result in a shunting of blood from the ischemic occluded extremity to the normal extremity thereby aggravating the ischemia

Uses and Limitations —Beneficial results from vasodilator drugs are obtained *most frequently in those conditions in which reduced regional blood flow is due to* functional vasoconstriction resulting from increased activity of the sympathetic nervous system i e Raynaud's phenomenon These agents tend to block the most active components of the sympathetic system The vasodilator effect can also be concentrated in a specific vascular bed by the intra arterial injection of some of the adrenergic blocking agents Occasionally this approach is useful as an adjunct to surgery i e to ascertain the level of a localized vascular occlusion or to predict the feasibility of sympathectomy

In general *long term* treatment with vasodilator agents is undesirable However continuous medication may become necessary in some instances Such a program is usually resorted to in conditions involving more than two extremities, fol

Adrenergic Blocking Agents—These compounds act directly on the blood vessels blocking the transmission of vasoconstrictor nervous impulses from the sympathetic nervous system to the smooth muscle in the vessel wall The more important compounds useful for this purpose are azapetine (Ilidar), phenoxybenzamine (Dibenzyline), tolazoline (Priscoline), and phentolamine (Regitine) In addition, Hydergine and hydralazine have some adrenergic blocking properties Recently, nylidrin (Arlidin) has been reported to produce selective vasodilatation in the skeletal muscles by direct action on the arteriole rather than by adrenergic blockade

TOLAZOLINE (PRISCOLINE) —*Tolazoline* is a peripheral vasodilator and adrenergic blocking agent, but it has many other actions Although the drug is a peripheral vasodilator, it may increase the pulse rate and the cardiac output similarly to a sympathomimetic agent, thus accounting for some of the cardiac side effects caused by it It may precipitate palpitations and anginal attacks It increases the myocardial response to epinephrine, and myocardial infarctions following the administration of tolazoline have been reported Other side reactions consist of shivering sensations, flushing of the face and neck, and conjunctival injection The drug has a variable effect on arterial blood pressure, sometimes increasing it and sometimes decreasing it

PHENTOLAMINE (REGITINE) —*Phentolamine* is one of the imidazoline series similar to tolazoline Unlike tolazoline, however, this agent is more specific in its adrenergic blocking properties and does not exert sympathomimetic effects It blocks both circulating norepinephrine and epinephrine vasopressor effects Its actions appear to be similar to phenoxybenzamine (Dibenzyline) When taken orally it produces nausea vomiting, and diarrhea in a very high percentage of patients Consequently, it is administered primarily by the parenteral route

AZAPETINE (ILIDAR) —Azapetine is also an adrenergic blocking agent which blocks sympathetic vasoconstrictor impulses at the blood vessels It has minimal effect on blood pressure although occasional patients may get a significant reduction Nasal congestion, vertigo drowsiness, and conjunctival injection are observed with its use

PHENOXYBENZAMINE (DIBENZYLINE) —This agent has a definite hypotensive effect when given in adequate doses Fatigue and orthostatic tachycardia may be observed Green found azapetine and tolazoline to be superior to phenoxybenzamine as vasodilators in normal volunteers While phenoxybenzamine was more effective in the hands than in the feet, it was, nevertheless, relatively ineffective in both The dose must be adjusted carefully so that an excessive blood pressure reduction is not produced Nausea pallor, and tachycardia are symptoms produced by an excessive reduction in blood pressure

Drugs Acting Directly on the Smooth Muscle of the Arterioles—There are several well known agents which act directly on the arteriole, producing vasodilatation The most important of these are histamine, nylidrin, papaverine and nitrites

HISTAMINE —This drug acts directly on the smooth muscle, producing vasodilatation It must be given in a very dilute solution intra arterially in order to

can be divided into three groups by virtue of their site of action (1) centrally acting agents, (2) ganglionic blocking agents, and (3) adrenergic blocking agents which block sympathetic impulses at the blood vessels Generally speaking, the adrenergic blocking agents are most useful for the treatment of peripheral circulatory diseases

Centrally Acting Agents —These consist of the rauwolfia compounds, hydralazine (Apresoline), and Hydergine In large doses the latter two also have peripheral adrenergic blocking activity In my experience, the centrally acting drugs are of limited use, being effective only in those diseases in which the vasoconstriction is on a functional basis such as in Raynaud's disease These compounds are of little or no benefit in vascular diseases in which there is anatomical damage to the vessels

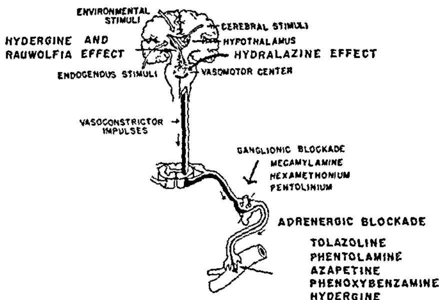


Fig 21 —Diagram of the autonomic nervous system and the point of action of the various drugs which block sympathetic nervous system impulses, i e, centrally acting agents, ganglionic blocking agents, and adrenergic blocking agents

Ganglionic Blocking Agents —These compounds, e g, hexamethonium, pentolinium mecamylamine, and chlorisondamine, effectively block the transmission of vasoconstrictor impulses over the sympathetic nervous system, but at the same time they block impulses going over the parasympathetic nervous system, and consequently side effects are numerous The chief untoward side effects are orthostatic hypotension constipation, decreased salivation, and inability to focus the eyes These side effects ...
the administration ...
more effective thar ...
are usually preferable

the symptoms of the two since they are both dependent upon a sudden interruption of blood flow to an affected area Naturally, the level of occlusion will determ ne the ability of collateral circulation to develop Usually, the more rapidly the *occlusion develops* the greater will be the associated vasospasm When partial occlusion exists for a sufficient time prior to complete occlusion collateral blood supply will frequently have developed and associated vasospasm is less prom nent

Embolism —The heart is the chief source of emboli, most commonly a de ached thrombus or portion of a thrombus which develops during auricular fibr l ation Myocardial infarction with mural thrombi, cardiac valvulitis in acute or ubacute bacterial endocarditis and thrombosis of the wall of the heart attributable o a failing heart from any cause may give rise to emboli which detach In ad lition, thrombi on the walls of the arteries carrying the systemic circulation may ive rise to emboli These develop in aneurysms on arteriosclerotic plaques and s a result of injury or inflammation Emboli tend to lodge where the artery sud enly becomes reduced in caliber, ordinarily at points of bifurcation or compress on n the arterial tree

Thrombosis —Acute arterial thrombosis may occur in the presence of ob ious peripheral vascular disease, as a result of direct trauma or contusion of the essel wall as a sudden occlusive thrombus in a previously unrecognized aneurysm r finally as simple arterial thrombosis in which all embolic and local vascular actors are absent Sudden arterial thrombosis occurs in about 10 per cent of ases of thromboangiitis obliterans, and also occurs with hemoglobinopath es epticemia, and chronic debilitating diseases Obviously under such circumstances ie prognosis as to life and limb is dependent upon the underlying disease processes esponsible for occlusion and upon the early institution of treatment

Treatment —The use of drugs in acute arterial occlusive disease is for tem orary expediency only If embolectomy and/or thromboendarterectomy are feasi le treatment should be primarily surgical with the least possible delay Vaso- ilator drugs serve two purposes in this condition to define more clearly the level f the occlusion to relieve the powerful reflex vasoconstriction in the collateral ves ls adjacent to the area of occlusion as well as in the major pathway itself We ave found that the agents of choice for these purposes are the adrenergic blocking gents tolazoline (Priscoline) and phenotolamine (Regitine) Intra arterial in ction above the site of occl ision is preferable (see page 491)

When the acute occlusive disease is diffuse and nonoperable intra arterial in ction may be followed after 2 or 3 days with oral medication Probably phenoxy enzamine (Dibenzyline) or azapetine (Ilidar) is preferable for this purpose It necessary to titrate the dose of these drugs for each patient (see page 491)

Raynaud s Disease and Other Vasospastic Conditions —

Raynaud s Disease —Raynaud s phenomenon is an episode of constriction of ie small arteries or arterioles of the extremities resulting in intermittent changes color of the skin of the extremities such as pallor and cyanosis *Following* the isode of constriction hyperemia may produce a red color This phenomenon ay occur primarily as in Raynaud s disease or it may occur in association with number of conditions and diseases and hence is no particular indication of the atus of the peripheral vascular system

minimize systemic reactions consisting of headache tachycardia bronchospasm hypotension and sometimes shock

PAPAVERINE —This drug acts directly on smooth muscle to induce relaxation It has not proved very effective

NITRITES —Nitroglycerin has been reported by Burke and his associates to produce increased blood flow through the extremities This response is reported to be associated with an increase in cardiac output In our experience the nitrites have been unpredictable in their effect on patients with peripheral vascular disease [Their use for dilatation of the coronary arteries is discussed in Chapter 24 Ed]

NYLIDRIN (ARLIDIN) —This is an epinephrine type compound which acts directly on the arterioles, producing dilatation It appears to be selective for the vessels of the skeletal muscle The drug has been reported to increase peripheral blood flow and exercise tolerance in patients with peripheral vascular disease, especially in patients with intermittent claudication

Nylidrin increases cardiac output and may on occasion precipitate angina in patients with coronary artery disease Anxiety and palpitations have also been observed

CLINICAL CONDITIONS AND THE USE OF VASODILATOR DRUGS

The term peripheral vascular disease is a general term which has led to much confusion in the diagnosis of diseases of the peripheral blood and lymph vessels As a group of individually distinct diseases their diagnosis depends upon a careful analysis of the history of the illness an appreciation of specific findings during the general physical examination and finally the application of a rather limited number of specific diagnostic techniques It is not the purpose of this writing to discuss the varied features of peripheral vascular disease and no attempt will be made to proceed further than a brief description of basic pathologic findings and the disturbance in physiology as it applies to therapy with vasodilator drugs The various conditions responsible for arterial insufficiency are discussed as follows

- Intra arterial occlusive conditions
  - Embolism ✓
  - Thrombosis ✓
- Functional vasospastic diseases
  - Raynaud s disease ✓
  - Raynaud s phenomenon in associated conditions ✓
  - Acrocyanosis ✓
- Morphologic occlusive disease involving the arterial wall
  - Arteriosclerosis obliterans
  - Thromboangiitis obliterans
- Post frostbite syndrome ✓
- Causalgia ✓
- Venous thrombosis and thrombophlebitis
- Delayed wound healing

Intra arterial Occlusive Conditions —Sudden arterial occlusion may be the result of either embolism or thrombosis There is no functional difference between

ically to designate a degenerative arteriopathy producing insufficiency of the arterial system The most common lesion producing occlusion of arteries is atherosclerosis with thrombus formation, although frequently a combination of atherosclerosis and medial calcification occurs in older individuals Occasionally, extensive calcareous deposits occur in the medial coat in the absence of atheroma The degenerative arteriopathies may be widespread, but both medial arteriosclerosis and atherosclerosis are essentially focal lesions The degree of ischemia produced by obstruction from arteriosclerosis obliterans may be augmented by arteriolar constriction from any cause and in such instances may be lessened by arteriolar dilatation with vasodilator drugs Sympathectomy and vasodilator drugs are indicated when the disease process is diffuse or small arteries are occluded When the lesion is localized in a larger artery, surgery, establishing a vascular bypass of the obstructed area is the procedure of choice

In general, arteriosclerosis obliterans is a progressive, degenerative disease and the long term prognosis for survival of the extremity affected by this disease is not good Unfortunately, life expectancy is also reduced, for the factors which produce arteriosclerosis of the lower extremity are likely to lead to similar lesions in other parts of the body, and sooner or later coronary or cerebral atherosclerosis usually develops and, less commonly, peripheral arterial aneurysm or abdominal aortic aneurysm There are, however, many extenuating factors which vary greatly in individual cases and the prognosis directly depends upon the stage at which proper treatment is instituted, extent of arterial occlusion rapidity of development, presence of collateral circulation, and complicating and associated diseases of other organ systems

THROMBOANGIITIS OBLITERANS—Thromboangiitis obliterans (Buerger's disease) is an inflammatory condition of the arteries adjacent vein, and nerve of the extremities resulting in obliterative occlusion which is frequently segmental The lower extremities are more commonly involved and usually more severely In the great majority of cases the disease begins in medium sized arteries or small arteries i e posterior tibial, radial, ulnar, plantar, palmar, and digital Large arteries, such as the femoral and brachial, are affected only late and only when the disease is severe and progressive Involvement of the veins is less common than involvement of arteries Small and medium sized veins are chiefly involved and large venous trunks are rarely affected

The striking physiologic change in thromboangiitis obliterans is the local impairment of arterial blood flow with reduction particularly in the more distal portion of the limb Another factor which contributes to the severity of the ischemia is arteriolar spasm Only this component of the disease is benefited by vasodilator drugs In general the more severe and more extensive the arterial occlusive disease, the less the possibility that the arterial circulation may be improved by a vasodilating procedure

The clinical course of the disease is episodic, characterized by exacerbations with some tendency to slow improvement between exacerbations, but the lesions are organic and produce permanent arterial occlusion The course thus depends upon the rapidity of development and extent of arterial lesions versus the development and capacity for blood flow in anastomosing arteries In general the

The diagnosis of Raynaud's disease should be limited to those cases exhibiting Raynaud's phenomenon and demonstrating the typical changes of the extremity in which the initiating lesion is not a morphologic change in the vessel. The cause of the attacks is considered to be either an increased local sensitivity to stimuli which normally produce vasoconstriction or a pathologic reinforcement of the reflex mechanism which responds to the stimulus. The underlying cause of this remains unknown. Greater emphasis has been placed on the bilateral symmetrical cutaneous gangrene which occurs in the absence of demonstrable organic arterial disease than on the less spectacular and less serious color changes which occur on exposure to cold or during emotional upsets. The disorder may remain rather stationary for a period of years but it tends to get progressively worse. Rarely is spontaneous improvement noted. Raynaud's phenomenon in the progressive or advanced stages of Raynaud's disease may be so severe and may appear so frequently that it is disabling. Sclerodermatous changes of considerable degrees in the skin of the involved parts may interfere considerably with normal use of the extremity, particularly of the fingers.

Raynaud's phenomenon may also be associated with a variety of contributing conditions and diseases. Among these may be mentioned (1) trauma including occupational and surgical injuries, (2) neurogenic origin including cervical rib, scalenus anticus syndrome, and costoclavicular syndrome, (3) intoxication by heavy

condition characterized by painless and *persistent* coldness and cyanosis of the distal parts of the extremities. The mechanism producing the vascular changes is not clearly understood. Trophic changes, ulceration and gangrene do not occur and examination of peripheral arteries will not reveal any evidence of occlusive arterial disease.

Sympathicotonia.—Disorders associated with increased sympathetic activity are the most amenable to therapy. Phenoxybenzamine, tolazoline, and azapetine given orally are all useful agents in this condition. Patients who respond to these adrenergic blocking agents will usually respond to sympathectomy, particularly if confined to one extremity. Phenoxybenzamine (Dibenzyline) may be superior to tolazoline and azapetine. When the drugs are given parenterally, tolazoline is the drug of choice. The ganglionic blocking agents have also been reported to be effective for this condition, but we feel that these agents should only be resorted to when the adrenergic blocking agents have failed.

The centrally acting agents may be of considerable value in the therapy of the vasospastic conditions by central depression of vasoconstrictor impulses. The rauwolfia compounds and Hydergine are the only useful drugs in this class for the therapy of vasospastic states. Occasionally improvement may be dramatic. The virtue of these drugs, when effective, is the low incidence of side effects and minimal hypotensive response. The rauwolfia compound selected can be given orally whereas Hydergine must be given intramuscularly.

Morphologic Arterial Occlusive Disease.—

Arteriosclerosis.—Arteriosclerosis obliterans is a descriptive term used clin

found that in 25 patients with causalgia who were given phenoxybenzamine or hexamethonium 6 had permanent and complete relief even after the drug was discontinued, 13 patients experienced complete relief while taking the drug 3 obtained partial relief, and in 3 there was no relief Phenoxybenzamine was found to be an accurate method for predicting the anticipated response to surgical sympathectomy

Venous Thrombosis and Thrombophlebitis—Vasodilator drugs are of little value, although some investigators have noted symptomatic improvement following sympathectomy

Delayed Wound Healing—Phenoxybenzamine (Dibenzyline) is effective here if any drugs are effective This drug acts by increasing circulation to the skin which may be of value if skin ischemia is a factor

THE ADMINISTRATION OF DRUGS USED FOR THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

The patient with peripheral vascular disease of the extremities will frequently have vascular disease elsewhere, particularly those patients with arteriosclerosis Therefore associated coronary sclerosis is common The therapeutist should remember this when prescribing drugs since so many of them have secondary cardiac effects which could be disastrous

Also the therapeutist must remember that vasodilator drugs are also hypotensive and the greatest degree of vasodilation will occur in those vessels which are most elastic and resilient Thus, if a blood vessel is organically damaged, it is not likely to dilate significantly It is only the collateral vessels which may be in a state of increased tone that the therapeutist can expect to dilate with vasodilator drugs Systemic administration of vasodilator drugs may decrease blood flow to the surgically sympathectomized extremity for this reason

Centrally Acting Agents—As indicated previously, the only indication for the use of the centrally acting vasodilator drugs is the treatment of functional vasospastic conditions The only centrally acting drugs that seem to have any merit are the rauwolfia compounds These agents depress the sympathetic nervous system centrally One of the following rauwolfia materials should be given orally

Reserpine 0 25 mg twice a day
Alseroxylon—2 mg twice a day
Whole root of *Rauwolfia serpentina*—50 mg twice a day

Ganglionic Blocking Agents—There is little indication or basis for the use of these drugs in the therapy of peripheral vascular disease However, when the therapeutist does use these drugs they can be given orally or parenterally When the parenteral route is used, it is for short term use only, and hexamethonium given intramuscularly is the agent of choice When given orally, the agent of choice is pentolinium

The initial dose of hexamethonium given intramuscularly is 15 mg This should be given every 4 to 8 hours If the response to 15 mg is not adequate the subsequent doses should be increased in 15 mg increments to a maximum of 50 mg per dose or until excessive orthostatic reduction in blood pressure occurs

collateral circulation about obstructed lesions in patients with thromboangiitis obliterans is better than around similarly obstructed areas in patients having arterio sclerosis Fortunately, there is a tendency toward ultimate cessation of develop ment of arterial and venous occlusion and, if this stage may be reached without the loss of digits or legs the outlook improves In contrast to arteriosclerosis oblit erans, this disease is essentially one of young adults with good capacity for tissue healing and repair, and the majority of patients seem to be singularly free from other nonvascular diseases The prognosis as to loss of limbs or portions thereof is difficult to estimate The actual incidence of all varieties of amputations seems to vary from 30 to 60 per cent depending upon the duration of the disease and whether patients are supervised, restrict their activity, and persistently follow a good therapeutic regimen Sympathectomy may prove to be very effective in some patients

Drug Therapy in Occlusive Vascular Disease —The chronic obliterative arterial diseases demand very careful treatment There is no widely accepted method of management of intermittent claudication Treatment is fraught with controversy and management is difficult at best Therapy is generally directed toward the relief of claudication However, although frequently disabling, claudication in itself is not the specter of the disease, but the chief danger lies rather in the decreased blood supply to the skin Therefore, treatment should be directed not only toward the relief of claudication but also toward the prevention of gan grene When patients do not obtain an adequate response to sympathectomy, vasodilator drugs may be used the results are variable

Moser and his associates have found that improvement in peripheral circula tion was more marked after hexamethonium intravenously than after tolazoline intra arterially These investigators suggest that sympathectomy is indicated in any patient obtaining a significant response to these agents Since long term ther apy is required it is essential that a regimen be established which is easy to fol low Thus only vasodilator drugs which can be self administered are indicated Orally effective drugs are the agents of choice Hydergine has been used but it must be given by the subcutaneous route

Phenoxybenzamine (Dibenzyline) has been reported to be effective and at present is the agent of choice The degree of response will naturally depend on the extent of involvement and the amount of associated functional vasoconstric tion Patients with mild disease respond best and those with moderate disease respond erratically

Tolazoline (Priscoline) and azapetine (Ilidar) have been reported to be effec tive More recently, nylidrin (Arlidin) has been used Since it does not act by blocking sympathetic impulses but has been reported to have direct vasodilator action particularly in the vessels of the striated muscles, it may prove to be the agent of choice

Post Frostbite Syndrome —The symptoms of increased sweating burning of feet sticking sensation and increased susceptibility to cold are improved with tolazoline and phenoxybenzamine but the results are not very encouraging

Causalgia —Phenoxybenzamine is the agent of choice for this syndrome and has been proved to be quite effective in alleviating symptoms Fowler and Moser

obliterans Side effects to date consist of nervousness and palpitations The results with this drug in our hands have not been as satisfactory as those reported by others

The drug must be given orally and the dose titrated The initial dose is 6 mg given 3 times a day with meals This dose can be increased to as much as 24 mg given 3 times a day

Histamine —Histamine is given intra arterially The solution is made up by placing 2 75 mg of histamine acid phosphate in 500 ml of normal saline The solution is then administered with a mercury pump or by a syringe at the rate of about 40 to 60 drops per minute The method is cumbersome Side reactions are quite common and consist of headaches, nausea, tachycardia and occasionally hypotension when the drug is given too rapidly

SELECTED REFERENCES

Boyd A M Oral Dibenzyline in Senile Obliterative Arteritis, Lancet 271 869 1956

Clark J *Rational Treatment of Vasomotor Disturbances Involving the Upper Extremities* Am Surgeon 22 420, 1956

Fontaine, Rene Remarks Concerning Venous Thrombosis and Its Sequelae, Surgery 41 6 1957

Fowler, F, and Moser M Use of Hexamethonium and Dibenzyline in Diagnosis and Treatment of Causalgia J A M A 161 1051, 1956

Freedman

Green, H

Moser M

1953

Murphy, T, Haglin, J, and Felder, D The Effect of Generalized Vasodilatation Upon the Sympathectomized Extremity, Surgery 41 178 1957

Renner W F Medical Management of Arteriosclerosis Obliterans, Maryland State M J 5 731, 1957

Stallworth J, and Jeffords J Clinical Effects of Azapetine (Ilidar) on Peripheral Arterial Dis

Stein, I A odilator With Selective Action on

Wessler S 5

The initial dose of pentolinium given by the oral route is 20 mg given e 6 to 8 hours This should be increased at weekly intervals in increments of 20 until the desired effect is obtained or excessive orthostatic reduction in blood p sure occurs The maintenance dose is kept just below this level Cathartics sho be used freely whenever constipation is a problem

Adrenergic Blocking Agents —

INTRA ARTERIAL ADMINISTRATION —The agents useful for intra arterial inje tion are tolazoline (Priscoline) and phentolamine (Regitine) The dose of tolazc line is 50 to 75 mg dissolved in 5 to 10 ml of normal saline

We prefer phentolamine to tolazoline for intra arterial administration The dose of phentolamine is 5 to 10 mg given in 2 to 10 ml of normal saline When these drugs are given intramuscularly, the dose of phentolamine is 5 to 10 mg and the dose of tolazoline is 50 to 150 mg

ORAL ADMINISTRATION —*Tolazoline (Priscoline)* is usually given orally, start ing with a dose of 50 mg with each meal The dose should be progressively in creased until the desired effects are obtained or undesirable side effects supervene These consist of chest pain and coronary insufficiency in patients with coronary artery disease Less frequently, chilliness, nausea restlessness, increased sweating and palpitations are observed

Phenoxybenzamine (Dibenzyline) This drug should not be given paren terally as a therapeutic measure When given intramuscularly it causes pain and necrosis When given intravenously it can cause tachycardia and an excessive reduction in blood pressure for which there is no antidote By the oral route it is relatively easy to handle but the dose must be titrated The initial dose should be 10 mg given after meals twice a day The dose should then be progressively increased at weekly intervals until the desired response is obtained or the side effects become intolerable The usual dose is 60 to 100 mg per day Boyd has suggested that the maximum dose should be 60 mg

Untoward effects consist of weakness, lethargy, dizziness due to hypotension (orthostatic), tachycardia, palpitations, drowsiness stuffy nose, nausea and dry mouth Sometimes just a small reduction in the dose will greatly decrease the severity of side effects

Azapetine (Ilidar) Azapetine is an adrenergic blocking agent and may also be a direct vasodilator which can be given orally or intravenously When given intravenously the dose is 1 mg per kilogram of body weight in 250 ml of normal saline There are few if any indications for the use of this drug by this route ex cept for tests of therapeutic efficacy or acute vasospastic states and acute arterial occlusion When given orally the dose should be titrated starting with 25 mg given 3 times a day The dose should be increased in 25 mg increments until relief of symptoms is obtained

Nylidrin Hydrochloride (Arlidin) This drug acts by direct vasodilation of the vessels supplying striated muscles It has little, if any, effect on the skin circula n It may be effective in obliterative disease of the arteries especially in pa nts with intermittent claudication since it increases muscle blood flow Thus it ndicated in patients with peripheral vascular disease associated with diabetes mbophlebitis thromboangiitis obliterans, ischemic ulcers and arterioscler

symptom can be obtained from a survey of the incidence figures for chroni bronchopulmonary disease in the United States in which cough is an invariable cor comitant The *National Health Survey of 1935-1936* showed that 1,700 000 per sons had chronic bronchitis and 1,150,000 had chronic sinusitis To these must b added the 3 to 4 million people who are afflicted with bronchial asthma, bronchi ectasis, and pulmonary emphysema These data become even more impressiv when it is realized that 13 per cent of the population of this country will be ove 65 years of age at the end of this century, and of these 13 per cent, it is estimate that 6 per cent will be chronic coughers" as a result of chronic lung disease

The common occurrence of cough in the acute respiratory diseases has mad cough remedies an indispensable item in the household medicine cabinet along wit aspirin and bicarbonate of soda Before considering the various pharmaceutica agents which suppress cough, a discussion of the etiologic factors and physiologi mechanisms involved in coughing is desirable if adequate and efficient managemen is to be achieved

The causes of cough are so numerous that they are difficult to classify Be cause of its wide distribution throughout the population, cough is often taken for granted by the patient and paid scant attention by the physician

Etiologic Factors —A classification based on etiologic factors includes

INFECTIOUS

Viral Common cold, influenza, atypical pneumonia, measles psittacosis etc
Bacterial Pneumonia, diphtheria, tuberculosis, pertussis, tularemia bubonic plague
Rickettsial Q fever
Mycotic Actinomycosis, blastomycosis coccidioidomycosis histoplasmosis moniliasis
Spirochetal Vincent's infection
Parasitic Ascariasis, oxyuriasis, distomiasis

IRRITATIVE

Mechanical Foreign bodies, retained secretions excessive strain or improper use of voice
Chemical Smoke, fumes noxious gases
Thermal Exposure to marked variations in temperature

ALLERGIC —Asthma hay fever vasomotor rhinitis

NEOPLASTIC

Intraluminary benign, malignant
Extraluminary with compression lymphomas, Hodgkins etc

VASCULAR —Congestive heart failure, aneurysm, embolism, pericarditis

PSYCHOGENIC —Tension, habit spasm or ' tic, ' psychoneurosis

The recognition of the causative factor initiating the cough reflex is of primary importance if appropriate measures, either medical or surgical, are to be instituted Although the investigation of the cause of cough is often difficult and complex, the following pertinent inquiries are helpful in defining the nature and hence the etiology of the cough (1) duration of the cough, (2) association with an acute

THE CHOICE OF ANTITUSSIVE AGENTS

Hylan A Bickerman, M D

INTRODUCTION

In pursuing its primary function of gas exchange, the lungs normally ventilate from 600 to 1,000 cubic feet of air daily Because of its exposed position with respect to the external environment, the lung is endowed with an elaborate protective mechanism which efficiently cleanses, humidifies, and warms the inspired air In spite of exchanging enormous quantities of air laden with particulate matter, noxious gases and fumes, and microorganisms, the lower respiratory tract remains sterile Any disturbance in these mechanisms for self cleansing frequently results in respiratory disease

The factors concerned with bronchoelimination are integrated by reflex activity so that gas exchange so necessary to survival is not impeded The hairs at the entrance to the nasal passages serve as a gross filter and provide the first line of defense More important mechanisms which serve to protect the alveoli against inhaled foreign material and retained secretions are ciliary activity, mucus formation phagocytosis bronchoconstriction with peristaltoid contractions, and cough From a clinical standpoint, cough is probably the most prominent of the mechanisms concerned with bronchoelimination In emphasizing the protective nature of the cough reflex in this introduction to antitussive agents, it might be well to repeat the old aphorism that more people have died from an inability to cough effectively than from the act of coughing itself

CLINICAL CONSIDERATIONS

Since cough is a protective, physiologic reflex, it occurs in health as well as disease and is frequently the presenting symptom in a wide variety of pathologic states ranging from a mild to a serious and even fatal illness Because of its universality and the fact that most patients do not consider cough a serious enough symptom to seek medical advice, there are no available statistics regarding the true incidence of cough Nevertheless, some inkling of the importance of this

*The assistance of Miss Sylvia Itkin in preparing this chapter is gratefully acknowledged

phase, it is depressed and fixed but *rises sharply in the expulsive phase* The extent of this rise appears to be related to the intensity and character of the cough In ordinary coughing, it does not rise to its fullest height, but seems to act as a controlling mechanism determining the amount of abdominal pressure that is exerted upon the chest

When the intensity of the stimuli evoking the cough response is increased there are several expulsive efforts for a single inspiration with closure of the glottis *between each With severe irritation, the cough* becomes paroxysmal in character, and a series of short severe expulsive efforts are noted followed by a quick deep inspiratory gasp and again a series of coughs Under the *fluoroscope the* diaphragm can be seen to rise sharply for a short distance with each cough as the volume of the thoracic cage contracts

As the glottis opens, an explosive gust of air is expelled from the respiratory passageways at a high initial velocity This velocity is the resultant of the high intrathoracic to mouth pressure gradient, and the marked contraction of the tracheobronchial lumina, which reduces the cross sectional diameters of the bronchial tree *to between one third to one tenth of normal The velocity of escaping air* has been estimated to be 0 5 to 2 0 meters per second in the bronchioles and between 50 to 120 meters per second at the glottis Under special circumstances, the initial velocity of air expelled during a vigorous cough has approximated the speed of sound

In paroxysmal coughing provoked by severe irritation or bronchial obstruction or compression, efforts at expulsion become greater and greater accompanied by a progressive narrowing of the bronchial *lumina leading to localized or* diffuse bronchospasm This type of response, far from being a protective reflex, may actually cause serious alterations in cardiopulmonary function

The Regulation of Cough—Cough is a highly integrated reflex act which is partially under voluntary control This voluntary control is more complete than that which exists with other comparable reflex mechanisms such as sneezing or vomiting Although the cough center has been located in the medulla near the sensory portion of the vagus nerve and adjacent to the vomiting center, *the central* nervous system pathways for coughing have not been clearly elucidated In fact *little is known of the interactions between the cough center,* the respiratory center, and other reflexes associated with respiration

The afferent impulses which initiate the cough reflex may arise from many areas both within and outside of the respiratory tract including central stimuli which act directly on the cough center Normally, coughing is produced by the stimulation of the sensory endings of the glossopharyngeal and vagus nerves. The major reflexogenous zones and their nerve pathways are illustrated in Table 31

Infrequently, dyspepsia may provoke coughing by stimulating sensory fibers of the gastric branch of the vagus nerve From the clinical point of view, perhaps the most important cause of coughing outside of the respiratory tract results from the s ... cond t ons about the external
meat ... reign bodies, and even
eczer ... ularly in children
... ie sensitivity of the re

upper respiratory infection, (3) seasonal variations, (4) daily variation in intensity, (5) dry or productive and the character of the expectoration, (6) quality of the cough and whether associated with changes in voice, wheezing, or emesis

Although the protective aspects of the cough reflex have been stressed in the opening paragraphs of this chapter, there are numerous instances in clinical medicine when the continued propagation of this reflex may be harmful In many disease states such as pertussis pulmonary tuberculosis, chronic bronchitis, and obstructive disease of the tracheobronchial tree, the cough reflex becomes self perpetuating and the resultant severe paroxysms of unproductive coughing cause serious debilitation of the chronically ill patient The dry, hacking, irritative cough of some acute infections of the upper respiratory tract such as laryngitis and tracheobronchitis may in itself become a major factor in retarding recovery by causing loss of sleep, inadequate food intake, nausea, and emesis Furthermore, there is some experimental evidence that the inspiratory rush of air which accompanies the first phase of the act of coughing may actually spread the infectious material deeper into the finer ramifications of the bronchial tree Several authors have stressed the role played by chronic ineffectual cough in the causation of pulmonary emphysema

While measures to ensure correct diagnosis and treatment of the underlying cause hardly need any comment the importance of vigorous symptomatic control of certain instances of coughing from a public health standpoint requires further emphasis Droplet nuclei containing the infectious agent may be expelled for a distance of 15 to 20 feet following a cough and remain suspended for long periods thus serving as a primary factor in the airborne transmission of disease The significance of this factor in connection with the acute respiratory diseases (A R D) alone is impressive when it is realized that there is an average of 2 5 "colds" for every person in the United States each year accounting for the loss of over 100 million workdays

GENERAL PHYSIOLOGIC AND PHARMACOLOGIC CONSIDERATIONS

Before discussing the management of cough and the pharmacologic agents hich act as cough suppressants a brief review of the mechanics of coughing and regulation would be appropriate

The Cough Mechanism—Three chief phases have been described during the act of coughing (1) *inspiratory* a sharp deep inspiration ending with closure of the glottis, (2) *compressive* contraction of the muscles of the thorax and abdomen with the diaphragm fixed, resulting in a high but momentary increase in thoracic pressure, and (3) *expulsive* the rapid expulsion of air at high velocity hen the glottis opens

During the first stage, there is an increase in the vertical diameter of the chest elongation and widening of the entire tracheobronchial passageway Contraction of the expiratory muscles, especially abdominal, during the short compressive age tends to draw the sternum and ribs downward, decreasing the capacity thorax and thus applying pressure to the entrapped air within the lung ressure has been recorded as high as 80 to 160 mm Hg The diaphragm o regulate and adjust the expulsive efficiency of the cough In the second

PHARMACOLOGIC AGENTS EMPLOYED IN THE MANAGEMENT OF COUGH

The symptomatic management of cough is justified only when adequate investigative measures are undertaken to ascertain the etiologic factor While this is a relatively simple procedure in acute self limited infections of the respiratory tract the causative factors involved in chronic cough often prove much more elusive Nevertheless without this knowledge, appropriate therapy whether medical surgical, or psychological cannot be instituted to eradicate this symptom It is not the purpose of this chapter to discuss the many detailed therapeutic approaches to the correction of each disease entity which may cause cough, since this would entail a consideration of chemotherapeutic agents, antiallergic regimens cardiotonic drugs and specialized surgical techniques Since ' time is often of the essence particularly in the debilitated patient and infant, the symptomatic control of cough is clearly indicated concurrent with more definitive therapy

Considerable disagreement and confusion has arisen over the basic classification and nomenclature of antitussive drugs first proposed by Brown in 1937 and since published in many textbooks on pharmacology Expectorants were classified as (1) sedative—soothes acute inflammation by aiding the secretion of protective mucus, (2) stimulant—stimulates repair in chronic inflammatory processes within the respiratory tract and (3) anodyne—depresses the cough reflex by central inhibition Within the past two decades, the synthetic organic chemist has added to the number of cough suppressants which now total well into the hundreds This is further complicated by the fact that many cough remedies are mixtures The possible combinations are limited only by the knowledge and imagination of the physician and the ingenuity of the pharmaceutical industry' Despite the new drugs and advances in our basic knowledge concerning the cough, ' It seems to be a field in which polypharmacy and shotgun mixtures have enjoyed immunity from attack for it makes little difference what the ingredients are or how many are included if the mixture only expressed the art of mixing palatable materials '

In view of the increasing opposition to the term ' expectorant," a much more sound physiologic classification has been expressed by Gold It is well to confine the term cough remedy in a specific sense to a drug which acts to raise the threshold of the cough center in the central nervous system or acts peripherally in the respiratory tract to reduce the impulses which pass to this center, or a mixture which combines both actions"

Centrally Acting Antitussive Agents

To a large extent, most drugs which depress the central nervous system may influence the cough center in the medulla However, the drugs which have proved especially useful in diminishing the cough reflex by raising the central threshold for noxious stimuli consists of the narcotic antitussives and the nonnarcotic centrally acting cough suppressants

Narcotic Antitussives—Until recently the phenanthrene alkaloids of opium consisting mainly of morphine and codeine, have been the most effective and commonly used cough suppressants In fact these drugs together with narcotics synthesized from the opium alkaloids, constituted the only potent agents available

ceptor zones vary in different areas of the respiratory tract. Two types of receptors appear to be present. The mucosa of the larynx and trachea are most responsive to mechanical irritation with only a weak response elicited below the level of the main bronchi, whereas the sensitivity to chemical irritants extends throughout the tracheobronchial tree. Tolerance often develops on continued stimulation, resulting in a decrease in excitability of the cough reflex. In addition it would appear that the terminal bronchioles and alveoli contain few if any receptors since they are unresponsive to cough stimuli.

Table 31. Afferent Neurogenic Arcs Mediating the Cough Reflex

Receptor Area	*Nerve Pathway*
External meatus of the ear	Auricular branch of vagus (Arnold's nerve)
Pharynx	Afferent fibers of glossopharyngeal and pharyngeal branch of vagus
Larynx	Superior laryngeal branch of vagus
Trachea, Bronchi, Pleura	Afferent fibers of pulmonary branches of the vagus
Diaphragm, Pericardium	Afferent fibers of the phrenic nerve; Cardiac and esophageal branches of the vagus

Respiratory Tract Fluid.—Since the cough reflex is intimately concerned with the expulsion of secretions within the respiratory tract as well as irritants, the nature of the respiratory tract fluid and the alterations produced by disease states and pharmacologic agents are of considerable importance in any discussion of antitussive drugs. The glandular cells lining the respiratory tract normally secrete a lemulcent lubricating fluid that serves to protect the lungs by trapping particulate matter and microorganisms. The alveoli and terminal bronchioles form a uick scanty secretion diluted by a more watery secretion from the glands of the onchial mucosa. Normally four factors are concerned with propelling these retions toward the glottis where it is either expectorated or swallowed. These lude (1) bronchiolar constriction or peristaltoid movements, (2) movement of during the respiratory cycle, (3) alterations in bronchial dimensions with uration, and (4) ciliary activity which propels the secretions forward at a rate to 3 cm per minute. These secretions are composed of 5 to 6 per cent solids er cent of which is mucin.

Three types of sputum have been reported by Basch, Holinger and Poncher result of studies on patients with bronchiectasis. The first portion of sputum coughed up is a bronchial mucus plug which is highly viscous and not ordi affected by expectorant agents. The second type is a liquefied fraction with cosity. Liquefaction of this portion results from the secretion of fluids from nchial glands, resorption of solid constituents and bacterial and enzymatic

The expectorant drugs act mainly on this second type of sputum by de its viscosity and thus rendering it more fluid and less tenacious. The third sputum occurs in the most dependent portions of the respiratory tract and coughed up. It has a high viscosity which is unaffected by drug or aerosol

codeine with fewer side effects Even if this be so, it is quite obvious that the common practice of prescribing multiple dose *quantities would make the dispensing* of morphine especially hazardous

CODEINE DIHYDROCODEINONE, AND PHOLCODINE —In general while these drugs are weaker antitussives than the morphine group, they have been widely employed as cough suppressants because of the lower incidence of adverse side reactions

Codeine Codeine *is approximately* one quarter as depressant to respiration as morphine Furthermore, as the dose of codeine is increased, commensurate increase in respiratory depression does not occur In fact, large doses tend to stimulate the cerebral centers, causing excitement rather than depression Nausea vomiting and constipation are significantly less prominent than with morphine Codeine *in common with the other opiates*, exerts a '*drying action upon the* mucosa of the respiratory tract which may be of some advantage where excessive mucus or an actual bronchorrhea is present In disease states characterized by bronchospasm such as asthma and pulmonary emphysema the indiscriminate use of codeine may precipitate severe respiratory insufficiency resulting from the increased *viscosity of the bronchial secretions and suppression of the cough reflex*

Both tolerance and addiction occur with codeine and other members of this group While codeine addiction is thought of as being relatively infrequent among drug addicts since it produces little euphoria compared with heroin and morphine it might be well to point out that a survey published in the *United States Public Health Reports indicates that codeine addiction is not as rare as formerly* believed and occurs to a large extent among patients who have received the drug for a therapeutic purpose, principally as cough medication

Dihydrocodeinone Dihydrocodeinone (Hycodan Dicodid) is marketed as the bitartrate in oral tablets and in a syrup Pharmacologically it is more active than *codeine and as a consequence, possesses more addicting* liability than codeine In fairly extensive clinical trials, particularly in patients with chronic cough due to pulmonary tuberculosis it has been proved to be an effective antitussive agent superior in many ways to codeine because of the lower incidence of side effects Constipation nausea drowsiness and vertigo were reported as being minimal with this drug as compared with codeine Occasional nausea has been noted when Hycodan was administered on an empty stomach At the customary dosage level of 5 to 10 mg 3 or 4 times daily, rapid and effective relief of cough is obtained, lasting as long *as 4 to 5 hours following a single dose At this dosage level, coughing was decreased* in frequency but not completely suppressed There was no difficulty in expelling mucus and retained exudate so that no significant interference with the elimination of secretions was observed Some dryness of the pharynx and occasional 'tightness' of the chest have been noted Despite the proved addiction liability of Hycodan, a number of *clinical reports take exception* by inferring that there is no evidence of tolerance, dependence, or addiction in patients treated with this drug for periods up to 32 months

Tussionex (ion exchange resin complex of dihydrocodeinone) contains 5 mg of dihydrocodeinone in combination with 10 mg of phenyltoloxamine an antihistaminic *preparation in a resin complex* This has been shown to yield a uniform sustained release of antitussive agent over a period of 8 hours In a recent clinical

It has been estimated that over 25 per cent of the total medical supply of narcotics in the United States are employed as ingredients in cough mixtures A list of the narcotic drugs which have been used as antitussive agents and the "average" adult dose for cough suppression are shown in Table 32

Table 32 Narcotic Drugs Which Possess Antitussive Activity

Generic Name	*Trade Name*	*Average Adult Dose (Mg)*
Codeine		8 0 15 0
Morphine		2 0 3 0
lethylmorphine		8 0 15 0
ihydromorphinone	D laudid	0 5 1 0
ihydrocodeinone	Hycodan Dicodid, Tuss onex	5 0 10 0
orpholinylethylmorphine	Pholcodine	10 0
urified Opium Alkaloids	Pantopon	2 0 3 0
ethadone	Dolophine, Adanon Amidone	1 5 2 0
eperidine	Demerol	25 0 50 0
vorphan	Levo-Dromoran	0 5 1 0

Heroin, diacetylmorphine, was at one time widely employed for cough sup ssion but has not been included in the above table since it may not be used lly for any purpose in the United States As Diamorphine, it is incorporated in y cough remedies prescribed in Great Britain and the Commonwealth nations The major therapeutic effect of most of the members of this group of drugs is elief of pain which is discussed in Chapter 12 To a greater or less degree of the drugs in the narcotic group affect respiratory activity and the reflexes ated with respiration This is primarily one of depression as a result of direct on the medullary centers With respect to potency both as analgesics and ssives, the natural and synthetic alkaloids of opium may be divided into two

ORPHINE DIHYDROMORPHINONE LEVORPHAN AND PANTOPON —Although ex r greater cough suppression the clinical usefulness of these drugs as antitussives usly limited by adverse side effects involving the respiratory tract and other In addition to depressing respiration, these compounds cause constriction mooth muscle of the tracheobronchial tree, thus predisposing to broncho- particularly in allergic and asthmatic patients Other effects on the re tract include a reduction in the glandular activity of the bronchial resulting in a more viscid secretion, and partial paralysis of peristaltoid ts and ciliary activity Undesirable reactions from widespread effects on al nervous system and peripheral organs result in dulling of the sensorium, eadache, nausea and vomiting anorexia, and constipation The hazard ddiction is just as serious in the treatment of chronic cough as in therapy ief of pain Except for certain special circumstances which include (1) ociated with severe uncontrollable pain, i e, malignancy, pleurisy, rib ortic aneurysm, etc, (2) acute left ventricular failure associated with (3) the seriously ill, apprehensive patient in acute respiratory distress ary infarct, tension pneumothorax, etc, these potent narcotic agents ce in the management of cough There are some physicians who feel appropriately adjusted doses of morphine are more effective than

superior to codeine on a milligram per kilogram basis In severe asthma associ with *paroxysmal coughing*, 50 mg of meperidine administered orally after m and on retiring *frequently diminishes the* racking, spasmodic coughing and prov much needed relaxation This will be *discussed further in Chapter 29, The Ch* of Antiallergic Agents In general, respiration is not depressed at this do level However the author has observed marked depression of respiration in *patients* who exhibited drug sensitivity to meperidine Dizziness, nausea, and oc sional *vomiting may* be encountered in the ambulatory patient Although mep dine has less addiction liability *than morphine*, *tolerance* and habituation can cur and hence proper precautions must be observed *to prevent addiction in* treatment of chronic cough In our clinic, the use of meperidine is restricted t 3 to 5 day course of therapy

Nonnarcotic Antitussives.—While the narcotic agents discussed above are fective antitussive *drugs*, *all have the disadvantage* of being potentially addicti and most produce undesirable side effects when *administered at optimum dosa* levels or for long periods For the past decade or two, the National Resear Council's Committee on Drug Addiction and Narcotics, with the help of individ *investigators* and the medical research divisions of several pharmaceutical firm has been seeking *nonaddicting antitussive substitutes* for the opium derivatives recent years several new types of *compounds have been developed which are c* pable of increasing the threshold of the medullary cough center to afferent tuss impulses without the undesirable effects of the narcotics A list of the more com *monly* used nonnarcotic preparations is shown in Table 33

Although *d methadone and d isomethadone have* been *reported* as havin antitussive activity comparable to codeine in *dogs*, *these nonnarcotic* cogeners c methadone have not been adequately studied in man

Dextromethorphan.—Dextromethorphan hydrobromide (Romilar), the dex tro isomer of the methyl ether of levorphan, unlike its levorotatory congener pos sesses no *significant analgesic properties, exhibits no depressant effect on respira* tion and lacks addiction liability Extensive experimental and clinical studie with this compound have amply demonstrated its antitussive activity By the use of experimentally induced cough in cats, it was noted that Romilar increased the central *threshold* for the cough reflex The frequency of coughing was diminished but the amplitude *remained unchanged Furthermore, ciliary activity was not* inhibited at dose levels below 5 mg per kilogram In assessing antitussive activity in healthy human subjects stimulated experimentally by citric acid aerosols, sig nificant cough suppression was noted over a 4 hour period

Table 33 Nonnarcotic Antitussive Agents

Generic Name	*Trade Name*	*Average Adult Dose (Mg)*
Dextromethorphan hydrobromide	Romilar	10 20
Noscapine (Narcotine)	Nectadon	15 30
Carbetapentane citrate	Toclase	15 30
Caramiphen ethanedisulfonate	Toryn	10 20
Levo Propoxyphene		65 130
Benzonatate	Tessalon	50 100
Homarylamine		15 30
[illegible]	[illegible]	25

study by Cass and Frederik this sustained release preparation produced effective cough suppression over a 10- to 12-hour period following a single dose This possesses manifest advantages, particularly in suppressing distressing night cough

Morpholinylethylmorphine Pholcodine (morpholinylethylmorphine) is at present undergoing limited experimental and clinical trials in this country, although its properties as an antitussive have been studied in England and France By an experimental technique in cats, May and Widdicombe found that Pholcodine was "more active in blocking the expiratory efforts caused by an endotracheal foreign body than codeine, but less active than morphine, it differed from morphine and codeine in seldom causing respiratory depression and gave far more consistent results than codeine" Experimental studies in man in which the cough reflex was stimulated by inhaled citric acid aerosol and by the intravenous administration of lobeline demonstrated that Pholcodine has significant antitussive activity when compared with placebo and codeine controls The degree of cough suppression for 10 mg of Pholcodine appeared to be comparable to 15 mg of codeine and persisted over a period of 4 hours This has been confirmed in clinical trials on patients with cough due to various disease entities including chronic bronchitis bronchiectasis, asthma, emphysema, lung cancer, and the acute respiratory infections Toxicity studies indicate that Pholcodine is one-fifth to one seventh as toxic as codeine at the customary clinical dosage level of 10 mg, 4 times daily Adverse side reactions appeared to be significantly less with Pholcodine than with morphine or codeine There was no evidence of respiratory depression Except for occasional instances of mild sleepiness or lightheadedness, the sensorium was intact Gastrointestinal disturbances including nausea, anorexia, and constipation were considerably less than with comparable doses of codeine The Expert Committee on Drugs Liable to Produce Addiction of the World Health Organization expressed the opinion that Pholcodine "is not more liable than codeine to produce addiction and that it is less readily convertible than codeine to an addiction producing drug"

METHADONE AND MEPERIDINE —Two synthetic analgesic drugs not derived from the opium alkaloids but which show some of the pharmacologic properties of morphine are methadone and meperidine

Methadone Methadone (Dolophine, Amidone) is a potent antitussive equiactive to morphine in this regard The oral administration of 1 5 to 2 0 mg of methadone is as effective as 15 to 30 mg of codeine in suppressing the cough reflex However the addiction liability of methadone far exceeds that of codeine and so to a great extent the usefulness of this drug as a cough suppressant is subject to the same drawbacks as morphine Nevertheless, it should be pointed out that most of the other adverse side effects such as depression of respiration, nausea, dizziness, lightheadedness drowsiness and constipation are less than with morphine

Meperidine Meperidine Demerol) shares some of the pharmacologic activities of morphine and atropine Although some textbooks on pharmacology state that this drug does not depress the cough reflex, there is sufficient clinical experience to indicate that it is an effective agent in ameliorating spasmodic type cough ing particularly in asthma Furthermore experimental assessment in cats the ed

been limited to the acute type of cough associated with upper respiratory infections in which Toclase was administered for periods of 5 days or less. Additional data including controlled experimental studies in man and clinical trials in patients with chronic cough due to various disease states are necessary for a more complete evaluation of this drug as an antitussive.

CARAMIPHEN.—Caramiphen ethanedisulfonate (Toryn) is a nonaddicting antitussive agent with minimal adverse side reactions. It is not a depressant to the central nervous system or respiration and does not cause constipation. Experimental studies in cats indicated that the antitussive effect resulted from an increase in the threshold of the cough center to afferent impulses. As with Toclase, there have been too few controlled studies to be able to establish definitely the clinical usefulness of Toryn in the management of cough. Cass and Frederik found 10 mg of Toryn to be less effective in suppressing chronic cough than 10 or 20 mg of Romilar or 15 mg of codeine.

LEVO PROPOXYPHENE.—Levo-propoxyphene is a new nonnarcotic antitussive which has been studied over the past 2 years. Unlike the dextrorotatory preparation, it does not appear to possess any analgesic properties. Experimental studies in man with citric acid induced cough demonstrated significant cough suppression over a 4 hour period with the 65 mg dose being somewhat more active than 15 mg of codeine. Long-term clinical trials have been conducted on patients with chronic cough. At dose levels of 65 to 130 mg, moderate to excellent relief of cough was obtained in 75 per cent of the patients tested. This was comparable to the relief afforded by 5 to 10 mg of dihydrocodeinone. Moreover, the incidence of side effects was significantly less than with dihydrocodeinone, and chronic toxicity studies in patients receiving 250 to 300 mg daily for periods of 2 to 6 months have shown no deleterious effects. In addition, responsiveness to medication appears to be maintained with no development of tolerance.

BENZONATATE.—Benzonatate (Tessalon) is a unique nonnarcotic cough suppressant which appears to have both a central and a peripheral action. Experimental studies in animals showed effective inhibition of the transmission of stimuli within the central nervous system. Its principal effect, however, appears to be on the stretch receptors of the lungs causing alteration in inspiratory response to cough stimuli. It has been demonstrated that decreasing the inspiratory, or first, phase of cough results in striking diminution in the intensity of cough. This will be discussed further under Peripherally Acting Antitussive Agents.

HOMARYLAMINE.—Homarylamine (N methylhomopiperonylamine) is a new synthetic antitussive agent. Experimental studies in man employing the citric acid stimulated cough indicated that at 20 mg dosage levels it was approximately equiactive with codeine 15 mg. Furthermore, the time response curves were similar to that of codeine with the peak cough suppression occurring 2 hours after ingestion of the drug. Increasing the dosage did not appear to result in a proportional increase in antitussive potency. The preliminary results of clinical trials in patients with chronic cough showed moderate to excellent reduction in cough over a 3 to 4 hour period in approximately 75 per cent of the patients tested. Side effects at dosage levels up to 40 mg administered at 4 hour intervals have been negligible in this preliminary series.

Comparisons with other antitussives including codeine and placebo controls yielded good dose response relationships with 10 mg of Romilar equiactive to 15 mg of codeine In well controlled clinical studies by Cass and Frederik and others in a large series of patients with severe chronic cough of varied etiology, evaluations based on multiple observation periods attested to the antitussive effect of Romilar in which respect it ranked approximately as great as that produced by equal amounts of codeine Long term clinical trials have shown no addiction effects and no evidence of tolerance The incidence of adverse side effects has been remarkably low, being of the same order of magnitude as that obtained with placebo and considerably less than with codeine

NOSCAPINE —Of all the alkaloids in opium, noscapine (nectadon, narcotine) (6 per cent) is second only to that of morphine (about 10 per cent) As a member of the benzylisoquinoline group the pharmacologic properties of the former are quite distinct from the phenanthrene derivatives or narcotic alkaloids Noscapine in keeping with the other benzylisoquinoline alkaloids is not a narcotic and has no addiction liability At dosage levels within the therapeutic range it shows little or no effect on the central nervous system In animals toxic levels produce signs of excitation rather than depression It exhibits no analgesic properties and tends to stimulate respiration

Although noscapine is not a new drug and a great number of conflicting reports have appeared in the literature since 1821 concerning its pharmacologic properties no therapeutic applications for this compound were available until recently In 1952 Winter and Flataker demonstrated the antitussive effect of noscapine in guinea pigs and dogs exposed to inhaled irritants They also noted that noscapine appeared to suppress allergic cough produced in sensitized guinea pigs exposed o an aerosol of specific antigen These experimental studies were confirmed by onzett and Rothlin in animals and by Bickerman and Barach in man In con olled studies employing various dose levels of noscapine codeine and placebo antitussive effect of noscapine appeared to be equal to that of codeine Ex sive clinical trials by a number of investigators both in this country and abroad e shown that noscapine is a potent nonaddicting cough suppressant with minimal reactions No intolerance was observed even in doses as high as 90 mg daily a period of 4 to 6 weeks Constipation and other gastrointestinal reactions not encountered and expectoration was not inhibited Noscapine appeared particularly effective in the treatment of spasmodic cough Because of its marg n of safety it was possible to increase the dose in order to obtain a r antitussive effect for the control of severe paroxysmal coughing Further dose response curves showed increasing cough suppression as the dose was ed which persisted for as long as 6 to 8 hours in several instances Repeti ses frequently elicited an additive response

RBETAPENTANE Carbetapentane (Toclase) is a nonnarcotic antitussive hich is said to inhibit the hyperactive cough reflex by selective act on on ullary cough center In addition to its antitussive activity, Toclase has like and local anesthetic properties Experimental studies in animals indi t side effects were minimal and that cough suppression was equal to that

Few cl nical stud es have been reported in this country and these have

lungs Tessalon, a congener of pontocaine, has received extensive clinical study here and abroad where it has been shown to have excellent antitussive activity with little or no toxicity No side effects such as dizziness constipation gastrointestinal intolerance or depressive effects on respiration or the central nervous system were observed after prolonged therapy Aside from the relief of cough the sensation of dyspnea and tightness of the chest particularly in patients with bronchitis associated with bronchial asthma was relieved In a controlled study employing a placebo substitution technique, Tessalon was administered to patients with chronic cough accompanying bronchiectasis bronchial asthma, and pulmonary emphysema The author noted that approximately 70 per cent of the patients experienced moderate to excellent relief of cough It was of interest that benefit was greatest in those patients with clinically demonstrable bronchospasm and was accompanied by a mean increase of 20 per cent in the vital capacity A course of therapy consisted of 100 mg of Tessalon, 3 times daily over a 2 week period Where Tessalon appeared to be ineffective in ameliorating cough increasing the dose did not alter the response Adverse side effects occurred in 3 patients one complained of nasal congestion and two noted a pruritic, macular dermatitis which promptly subsided on withdrawal of the medication More recent studies employing experimentally induced cough indicated that Tessalon is effective in suppressing the acute cough due to pharyngeal or tracheal irritation, and compares favorably with the effect of 15 mg of codeine

Expectorants—*Agents which modify the output and viscosity of the respiratory tract fluid are designated as expectorants in the pharmacologic literature Unfortunately, the term* 'expectorant" *has led to considerable confusion in* classification, as has been remarked upon previously According to the dictionary expectorant" *is defined as "a tendency to facilitate the act of expectorating* If we accept Boyd s definition of expectorant as a drug which increases the output of *respiratory tract fluid, then such terms as stimulant expectorant and* sedative expectorant, still widely used in pharmaceutical classifications, are wholly misleading *Preparations which affect the respiratory tract fluid are* antitussive in that (1) by decreasing the viscosity of the bronchial secretions, their elimination is *facilitated so that the vicious cycle of ineffectual coughing is not perpetuated* and (2) by increasing the amount of respiratory tract fluid, a soothing or demulcent *action is exerted upon the mucosal lining thus relieving* the dry, unproductive cough due to irritation of the respiratory airway

Although the use of gargles, lozenges troches, and cough drops' is helpful in stimulating the flow of saliva and thus preventing the 'drying out' of the *pharyngeal mucous membranes, most of the* stimuli which give rise to cough originate in the lower respiratory tract, not reached by demulcent saliva Many of the *drugs which increase the respiratory tract fluid* and make the sputum more fluid and less tenacious are nauseants which, reflexly, increase the secretions within the *respiratory tract* This group includes the iodides, antimony and potassium tartrate, ammonium chloride, ipecac, emetine, and syrup of squill, and senega *In* addition to its nauseant action iodine is rapidly excreted by the bronchial glands and can be detected in the secretions within 15 to 25 minutes after oral or intravenous administration

DIMETHOXANATE.—Dimethoxanate (Cothera) is an alkyl ester of phenothiazine which appears to possess antitussive activity. It is nonnarcotic, and clinical trials have indicated that side effects are minimal. This preparation is devoid of central depressant or analgesic properties. The preliminary data suggest that 25 mg of Cothera has an antitussive potency equivalent to 15 mg of codeine. Further controlled studies are necessary to properly assess its place among the newer non narcotic agents.

Peripherally Acting Antitussive Agents

This class of drugs acts principally by decreasing the local irritation within the respiratory tract and thus reducing the tussal impulses which serve as the afferent arc for the cough reflex. A decrease in the impulse to cough may be effected locally by (1) the production of a mild analgesic or anesthetic action on the mucosa of the respiratory tract, (2) the reduction in the viscosity of the mucus within the respiratory passages so as to facilitate the evacuation of retained secretions, (3) the humidification of the respiratory tract, and (4) the relaxation of the smooth muscle of the bronchi in the presence of bronchospasm. Before discussing these drugs it should be made clear that with few exceptions, most of the agents in this category do not have specific local effects but tend to show considerable overlap. To a large extent our knowledge concerning the mode of action of many of these drugs is incomplete although syrups have been employed for the relief of ough for over four centuries. Whether by pharmacologic or psychologic effect elief of cough by any one of a multitude of aromatic syrups and elixirs has fforded increased comfort to the patient and hence these preparations have be me empiric remedies. While they may aid in reducing local irritation, most these agents are employed as vehicles for the more specific antitussive drugs dis sed in the preceding section.

Demulcents.—Demulcent preparations are bland substances which act by pro ively coating the irritated pharyngeal mucosa and possibly by exerting a mild gesic effect locally. Most of these preparations serve as vehicles for prescrip cough remedies and consist of syrup of acacia, glycerin, licorice, and wild y. Compound ether spirit and chloroform water have also been prescribed for their "expectorant" and local analgesic properties.

ocal Anesthesia.—The inhibition of the cough reflex by the instillation of l anesthetic agent into the respiratory tract is an important feature of cer ocedures such as bronchoscopy and bronchography. However, the instilla local anesthetics for the management of cough is impractical since it would ossible to anesthetize all of the receptors by this method. Animal experi ave demonstrated that the amplitude and frequency of coughing was modi large extent by the preceding inspiration. This is mediated by the Hering eflex whereby the stretch receptors within the lung modify the expiratory the act of coughing.

he past two years polyethylene glycol derivatives of p butylaminobenzoic been tested clinically for their effect on cough. These substances are hetics with an apparent selective effect on the stretch receptors of the

"Stimulant" Expectorants.—There are a number of substances, employed principally as vehicles in cough remedies, which have been used empirically to lessen the amount of mucus in chronic productive cough associated with chronic bronchitis bronchiectasis and lung abscess These have been classified in the older literature as 'stimulant expectorants' and are presumed to aid healing in the chronic stage of inflammation by producing a mild irritation Creosote preparations consisting mainly of calcium creosote and creosote carbonate have been used to decrease the amount of sputum and render its odor less objectionable Perhaps the best known member of this group is terpin hydrate There are considerable differences of opinion with regard to the mechanism of action of the terpins It is claimed that like other volatile and aromatic oils, terpin hydrate does not act reflexly upon the stomach but directly upon the secretory glands of the respiratory tract Rather than lessening sputum formation, Boyd states that it is a true expectorant' and increases the respiratory tract fluid From the clinical point of view, the average recommended dose of elixir terpin hydrate contains only 68 mg per teaspoon (5 ml) which is considerably less than the pharmacologically effective dose of 300 mg Its main action, therefore, is to serve as a pleasant tasting vehicle for more specific antitussives

GLYCERYL GUAIACOLATE.—Although the guaiacols are usually classified with the creosotes glyceryl guaiacolate (Robitussin) deserves mention Experimental studies by Boyd and his associates indicated that respiratory tract fluid was increased by almost 200 per cent following the administration of glyceryl guaiacolate, whereas the carbonate and sulfonate of potassium guaiacol were without effect The oral administration of these conjugated derivatives does not result in the appearance of guaiacol in the pulmonary passages, as has been observed after ingestion of the free guaiacol or its ethereal derivatives'

While it has been my general plan to avoid discussing mixtures of drugs of which there are many hundreds in this particular field of therapy, a fairly extensive literature has accumulated with respect to Robitussin (glyceryl guaiacolate 100 mg desoxyephedrine 1 mg in 5 ml of aromatic syrup) Studies in adults and children with cough due to a wide variety of disease states indicate that it is a highly effective antitussive with virtually no side effects It was felt that the clinical efficacy of Robitussin was for the most part due to the marked increase in respiratory tract fluid produced by the glyceryl guaiacolate which reduced the viscosity of these secretions It is doubtful whether a 1 mg dose of desoxyephedrine would have any significant bronchodilator effect on the smooth muscle of the tracheobronchial tree The aromatic vehicle would be expected to have an effect similar to other demulcents on the pharyngeal mucosa

Humidification.—It has long been recognized that cough may be materially decreased by proper humidification of the respiratory passageways In addition to providing a demulcent action of the mucosal surfaces, the respiratory tract fluid is increased thus lowering the viscosity of the bronchopulmonary secretions The clinical effectiveness of the steam kettle and croup tent have been well documented particularly in the spasmodic and croupy cough of children

Within the past two decades, new techniques employing aerosols have been developed which provide 'cold humidification" In addition to increasing the

Iodides—Salts of iodine have been used for over a century in the treatment of cough and bronchial asthma. Combinations of iodides with specific bronchodilator agents are frequently employed in the management of bronchospastic states such as asthma and pulmonary emphysema. This will be discussed in Chapter 29, The Choice of Antiallergic Agents. There are two types of iodide preparations. (1) Inorganic iodides, such as saturated solution of potassium iodide or syrup of hydriodic acid, are generally employed and, although they may impart a bitter, metallic taste, this can be partially concealed by prescribing them with milk or in various demulcent syrups. An initial dose of a saturated solution of potassium iodide, 0.5 ml., 4 times daily, after meals and at bedtime, gradually increasing to 1 to 2 ml., 4 times daily provides effective "expectorant" action. Enteric-coated tablets containing 0.5 Gm. and 1 Gm. of potassium iodide (Enkide) are available for patients who complain of gastric intolerance to the saturated solution. (2) Organic preparations such as Lipoiodine, Triode, Organidin, and Amend's solution are less irritating and are more acceptable as to taste than the inorganic iodides, but are absorbed more slowly.

The iodides may be given for long periods since tolerance rarely develops. Nevertheless, this drug in common with the other expectorant agents should not be prescribed for longer than is necessary once the cough has become quite productive. The usefulness of the iodide preparations is limited in a large measure by the unpleasant taste and the common occurrence of minor side effects which include coryza, acneiform skin eruptions, erythema of face and chest, and painful swelling of the salivary glands. These reactions quickly subside on discontinuation of the medication. True sensitivity reactions as denoted by fever, malaise, and generalized skin eruptions have been successfully treated by corticotropin and the adrenal steroids. The presence of inactive pulmonary tuberculosis does not contraindicate the use of the iodides despite such statements in the older literature. [H]obby believes that "the thinning out of the secretions (by iodides) produces more [spu]tum and floats out bacteria already present, but it does not cause reactivation or [spr]ead of the disease."

Ammonium Salts—Although the ammonium salts—chloride, carbonate, and [citra]te—are probably the most commonly used "expectorants," the amounts in[corp]orated in cough preparations are often less than the dose necessary to increase [respi]ratory tract fluid. Their action is transitory and "it is not unlikely that some [of the] beneficial action ascribed to ammonium salts is in reality due to the ingestion [o]f large amounts of water taken with these salts." (Goodman and Gilman.)

[N]auseants.—Of the nauseant compounds, ipecac is perhaps the only one which [merits] discussion. Perry and Boyd, and Basch and his co-workers found that [ipecac] induced a considerable increase in respiratory fluid secretion. Ratner re[ports] excellent results from syrup of ipecac in asthmatic children with inspis[sated m]ucus who were resistant to epinephrine. In tight croupy cough in chil[dren, em]etic doses of ipecac 0.5 to 2 ml. are frequently of valuable help in rid[ding the] bronchi of thick tenacious mucus. Ipecac also appears to relax the [smooth m]uscle of the bronchi and has been employed in our clinic chiefly in asthma[tics w]ho are hypersensitive to the iodides. The average "expectorant" dose in[this has] been 0.5 ml. 4 times daily.

bronchial tree (3) It is believed to have a local bronchodilator effect on the smooth muscle of the respiratory tract In effect, carbon dioxide inhalations modify the respiratory tract fluid and aid in the elimination of retained secretions These mechanisms serve to convert tussal insufficiency into an effective cough, particularly in the debilitated patient

Treatment is carried out by administering 5 per cent carbon dioxide in combination with 95 per cent oxygen at a rate of 5 to 7 liters per minute, by means of a mask or nasal catheter Each treatment consists of 10 to 15 minutes of gas inhalation repeated 3 to 4 times daily until cough is alleviated Since this technique for managing cough involves specialized apparatus and careful supervision of the patient, its usefulness has for the most part been restricted to the hospitalized patient

In addition, there are a number of contraindications which further limit its usefulness in certain disease entities associated with cough These include (1) cough due to pleural involvement, (2) recent evidence of hemoptysis, (3) diseases associated with an elevated pCO_2, such as pulmonary emphysema, severe bronchial asthma pulmonary fibrosis, etc, (4) systemic hypertension, and (5) cough originating outside the respiratory tract such as from aneurysms, irritation of Arnold's nerve etc

Radiation —In certain specialized instances, particularly in children where cough is the result of compression on the respiratory passageway by thymic enlargement or tracheobronchial lymphadenopathy, radiation therapy over the affected areas has been reported as beneficial when all other measures have failed The promiscuous use of irradiation for other disease entities such as asthma and infections of the lung in which cough is a prominent symptom can only be condemned in the light of more specific therapeutic measures for these conditions and the well known hazards of radiation

BASIC PRINCIPLES GOVERNING THE SELECTION AND USE OF ANTITUSSIVE AGENTS

While space does not permit detailed discussion of the best application of all the antitussive agents mentioned in the previous section certain basic principles are worth emphasizing to obtain maximum therapeutic effect with a minimum of undesirable side reactions Although pharmacists still stock a multitude of antitussive agents and mixtures many of which have been used on an empiric basis re evaluation of these drugs by controlled clinical and experimental techniques will eventually result in the discarding of many of the time honored mixtures and elixirs and permit more rational selection of the remaining pharmacologically active drugs

There is considerable justification in objecting to the current practice of ordering a fixed dose of an antitussive to be administered at stated intervals such as every 4 hours, etc Except in rare circumstances, cough is sporadic in character and, depending upon the causative factors, usually has well defined predilections time of day, degree of exertion changes in posture and that ever present scapegoat "the weather" Moreover, it is well recognized clinically that within certain limits increasing the dose results in little or no potentiation of the antitussive effect

moisture of the respiratory tract, aerosols may be used to administer various agents such as bronchodilators detergents, mucolytic preparations and chemotherapeutic substances The deposition of these therapeutic aerosols within the respiratory tract has provided a valuable approach to the treatment of many disease entities commonly associated with cough It is beyond the scope of this presentation to discuss the effectiveness of aerosol therapy in such conditions as tracheobronchitis, bronchiectasis lung abscess, sinusitis bronchial asthma, and pulmonary emphysema to mention a number of the more common disease entities in which cough is a prominent symptom However since aerosol therapy has assumed an important role in the management of certain allergic disorders of the respiratory system, a more complete discussion will be presented in Chapter 29, The Choice of Antiallergic Agents

Bronchodilators.—The cough and obstructive dyspnea of bronchial asthma and pulmonary emphysema which constitute the most distressing features of these diseases may be markedly alleviated by the proper use of agents which relax the smooth muscle spasm of the bronchial tree These bronchodilator agents may be separated into three categories sympathomimetics, parasympatholytics, and antispasmodics Although these agents together with the bronchodilator aerosols will be discussed in the chapter on antiallergic agents, it should be pointed out that many proprietary cough remedies contain drugs which fall into this group such as ephedrine phenylephrine theophylline, papaverine and atropine It is highly questionable whether any true bronchodilator activity is obtained with the average dosages recommended for these preparations

Antihistaminics.—Although not technically antitussives, the antihistaminic agents are mentioned briefly in this section because of their common usage with the bronchodilators in the treatment of allergic disorders Despite clinical evidence that the antihistamines, of which there are well over 100, are only indicated in certain types of cough occurring as a manifestation of allergy, many of these compounds have been incorporated into popular cough preparations Boyd observed that the cough of acute respiratory disease was not benefited by the antihistamines. He condemned the routine use of these agents in antitussive remedies Perhaps the popularity of these antihistamine antitussive preparations can be attributed to their "drying effect" similar to the effect of atropine derivatives on nasal and pharyngeal tissues In the "common cold," nasal congestion and pharyngeal secretions are diminished, adding much to the comfort of the patient. However, it should be emphasized that this "drying effect" may be deleterious particularly in patients with cough resulting from retained secretions These secretions become more viscid and may obstruct the smaller bronchioles, thus seriously interfering with bronchoelimination

Carbon Dioxide and Oxygen For the sake of completeness there are two additional procedures for the management of cough which deserve mention ... has enthusiastically advocated the use of inhalations of mixtures of carbon dioxide and oxygen The rationale of carbon dioxide inhalation is based upon the following principles (1) Carbon dioxide serves to liquefy bronchial secretions making them less viscid and more easily expectorated (2) It influences the depth of respiration thus increasing peristaltoid movements of the tracheo

author that the combination of an effective nonnarcotic centrally acting antitussive with a true "expectorant" would perhaps serve as a more rational approach to the management of cough

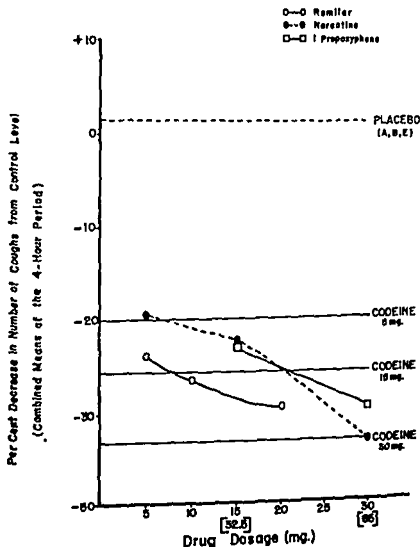


Fig 22 —Relative potency of Romilar, Nectadon (narcotine) and l propoxyphene compared with placebo and codeine, based upon the per cent decrease in cough frequency from the control level over the entire 4 hour period (From Bickerman, H A, et al Am J M Sc 234 191, 1957)

Of the peripherally acting agents with a local anesthetic effect, Tessalon deserves some comment It may prove to be a valuable adjunct, together with bronchodilator preparations, for the intractable chronic cough frequently encountered in such bronchospastic diseases as bronchial asthma and pulmonary emphysema. It should be pointed out that if no clinical benefit is derived after one week s trial, further therapy would prove worthless

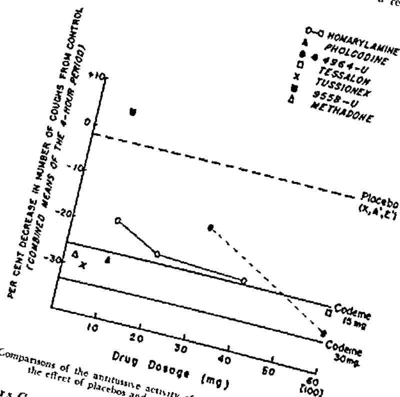
For example, in the treatment of the majority of patients with cough, 15 mg of codeine has far fewer side effects and is almost as effective as 30 mg

Of the centrally acting narcotic antitussives, the most widely used have been codeine and dihydrocodeinone With respect to these agents it has proved advantageous to employ smaller doses at more frequent intervals rather than a large dose infrequently In this connection the use of 10 or 15 mg of codeine for example every 2 hours has resulted in more effective control of intractable cough than doses of 30 to 60 mg every 4 to 6 hours In keeping with the more potent narcotic agents these drugs have well defined undesirable side reactions particularly when used in the treatment of chronic cough Gastrointestinal intolerance, constipation, central nervous system depression, and the development of tolerance and addiction liability are the major drawbacks in prolonged therapy A sustained release preparation such as Tussionex may overcome some of the drawbacks by providing effective cough suppression with minimal dosage since 2 tablets containing 5 mg each of dihydrocodeinone maintains antitussive activity over a 24 hour period

Recently as a result of intensive investigation nonnarcotic agents have been developed which compare favorably in antitussive effectiveness with codeine Since these agents are nontoxic and possess few if any, of the undesirable reactions characteristic of the narcotic agents it is my own opinion that in time these preparations will largely supplant the more popular narcotics employed today, except for certain special instances where analgesic and sedative euphoric effects are desired This would be pertinent to the use of morphine in the treatment of cough associated with malignancy or the use of Demerol in the tense, anxious patient with bronchial asthma Onset of cough suppression with these newer synthetic preparations is fairly rapid 20 to 30 minutes) with effectiveness persisting 4 to 6 hours Since they are virtually nontoxic these agents are especially suitable for prolonged therapy and in the treatment of children While the dosage in children is usually calculated on the basis of body weight more frequent or increased dosage has not resulted in any untoward effects The relative effectiveness of some of these agents as compared with codeine and a placebo are illustrated in Figs 22 and 23 These evaluations are based upon experimental studies employing citric acid induced cough

Although considerable doubt has been expressed within recent years on the value of so called "expectorant" agents in the treatment of cough there is sufficient evidence presented by Boyd and others to indicate that agents which increase respiratory tract fluid lower the viscosity of such secretions and in addition exert a demulcent effect on the bronchial mucosa The physiologic effect, then, would be one which favors the removal of these secretions and diminishes the tussal impulses arising from irritated areas within the respiratory tract From the evidence presented it would appear that humidification plays an equal role in producing these effects Indeed it is the opinion of many practitioners that the inhalation of steam or cold vapor by aerosol is the most efficacious measure in the treatment of nonproductive cough Of the agents which influence respiratory tract fluid only two are worth considering the iodides and glyceryl guaiacolate. In adding to the confusion which already exists with respect to the multitude of mixtures dispensed as cough remedies it seems quite appropriate to

Psychogenic Cough and "Night Cough"—The management of two special instances of coughing which have not been previously discussed are the cough of psychogenic origin and the 'night cough.' The pharmacologic therapy of psychogenic cough has been, on the whole, disappointing. As with the psychosomatic symptoms referable to other organs, any new preparation exhibits remarkable but, alas, only temporary benefit. In the treatment of this type of patient one must display his knowledge of the *art* of medicine in addition to his knowledge of rational pharmacology. There are several proprietary cough remedies, such as dihyprylone (Sedulon), which are purported to act as sedative antitussives for "night cough." Although there may be special merit for such preparations any effective cough suppressant combined with a suitable hypnotic may insure a restful night if administered prior to bedtime.



Comparisons of the antitussive activity of various drugs over a 4 hour period with the effect of placebos and codeine as standards of reference

…okers Cough—While an extensive literature has been devoted to the so… smoker's cough,' this term still remains ill defined and excites almost as …ntroversy as the role played by cigarette smoking as a causative factor in …is of lung cancer. In all probability this is not a single entity but com… …gh of varying etiology, such as chronic bronchitis, etc., which is undoubt…

edly aggravated by the inhalation of specific irritants, namely tobacco smoke and its accompanying combustion products While the cessation of smoking may improve such coughing clinically, the eradication of the underlying disease process together with appropriate symptomatic measures as outlined in the preceding sections are also necessary for adequate therapy

Since cough is a symptom complex which may arise from any one of a multitude of disease entities, treatment of the etiologic factors in itself is antitussive In the main, this chapter has dealt with the symptomatic control of cough by various

n "antitussive" requires

represents perhaps the

ned secretions In the presence of such secretions the ideal antitussive might well be one which, although reducing the number of ineffective coughs, permits an adequate flow rate in the remaining coughs so as to aid bronchial drainage In the absence of secretions when cough is purely irritative or reflex in character, a decrease in the frequency of coughs as well as the intensity would be desirable The ideal antitussive, furthermore, might effectively convert a nonproductive cough to a productive one by measures designed to increase the respiratory tract fluid and thereby reduce the paroxysmal character of such coughing

The search for the ideal antitussive has gained new impetus during recent years through the development of experimental techniques Prior to this, a review of the literature on the evaluation of antitussive agents disclosed that the majority of the reports were concerned with clinical appraisals in patients suffering from disease entities associated with chronic cough Since 1938, when Frnst first described an experimental technique for eliciting cough, a total of 21 reports on this method of assessing antitussive activity have been published Many of these experimental methods have been reviewed by Tiffeneau Of these, only 8 papers pertain to studies on human subjects

In keeping with the nonspecificity of this field of therapy, this discussion, of necessity, has been unduly lengthy Perhaps more than any other symptom, the treatment of cough emphasizes the art of the practice of medicine The rational approach to cough therapy is still in its infancy It is only within the past decade that a small beginning has been made in wedding the experimental approach to the well controlled clinical study which will ultimately quantitate the effect of pharmacologically active agents on the many variables of the cough mechanism Preparations assessed in this manner will not be empiric but will have well defined antitussive characteristics which can be integrated into a sound program for the management of cough

SELECTED REFERENCES

Abelman, W H Gaensler E A, and Badger, T L Clinical Evaluation of Toryn Dis Chest 25 532, 1954

Banyai A L. Fifteen Years' Experience With Carbon Dioxide in Management of Cough Dis Chest 13 1, 1947

Barach, A L, and Bickerman H A Pulmonary Emphysema Baltimore, 1956 The Williams & W...

l and Chemical Properties of Sputum rom Different Parts of the Tracheo

Bicker[illegible]

Ibid

Boyd,
Ibid
Browr
Cass,

Ibid Quantitative Comparison of Cough Suppressing Effects of Romilar
sives, J Lab & Clin. Med. 48 879, 1956
Ibid The Clinical Evaluation of Sustained Release Antitussives, Ann.
1958
Cass, L J, Frederik, W S, and Andosca, J B Quantitative Com
methorphan Hydrobromide and Codeine, Am J M Sc. 227 291,
Chakravarty, N K, Matallana, A, Jensen, R., and Borison, H L. Cent
tussive Drugs on Cough and Respiration, J Pharmacol. & Exper
1956
Denton, R Continuous Nebulization Therapy, Pediat. Clin North Amer
Douglass, B E Causes and Therapy of Cough, M Clin North Americ
Goodman, L S, and Gilman, A. The Pharmacological Basis of Thera
York, 1955, The Macmillan Company
Green, A F, and Ward, N B The Action of Analgesics and Nalorp
Reflex, Brit J Pharmacol 10 418, 1955
Hayes, E W
Chro
Hobby, ∖ W
Konzett, H
67 3
May, A I and W dd combe
Phillips
Ratner F
557, 1947
Tiffeneau, R La toux experimentale Methode de production Exposé a
11: 265, 1956
Tuft L and Levin, N M Studies of the Expectorant Action of Iod
203 717 1942
Van Dongen, K The Effect of Narcotine, Ticarda and Romilar on
Movements of the Cilia in the Air Passages, Acta physiol et p
500, 1956
Winter C A and Flataker, L Antitussive Compounds Testing Meth
Pharmacol & Exper Therap 112 99, 1954

THE CHOICE OF ANTIALLERGIC AGENTS

Hylan A Bickerman, M.D, and
Alvan L. Barach, M D.

INTRODUCTION

The scope of a chapter which discusses pharmacologic agents possessing anti allergic activity should include a precise definition of "allergic' phenomena In the past half century, since von Pirquet first coined the term "allergy' to describe the altered reaction of tissues to repeated contacts with infectious and antigenic substances, such as bacterial vaccine, tuberculin, and foreign serum, the newer concepts developed in immunology, biochemistry, and cytochemistry have extended the field of allergy into almost every pathologic process involving man In order to maintain the integrity of the "milieu interieur," various defense mechanisms some simple and others more elaborate, constantly guard against the impingement of a foreign or external environmental attack Reactions of the host have been noted to such influences, principally of a protein and carbohydrate nature, but often including organic compounds such as drugs or physical agents such as heat and cold Access through the various portals of the body have been observed, including the respiratory tract, the alimentary system, the skin and conjunctiva Allergic responses comprise the etiologic and pathogenetic bases for a wide variety of disease states The term "allergy' has been applied to a multitude of conditions in which the tissues or organs of one person respond to contact with some foreign material in a definitely different manner from the corresponding tissues or organs of other persons of the same species

The allergic reaction is highly specific, it implicates a precise antigen antibody type of reaction Most allergists use the term 'hypersensitivity" interchangeably with that of allergy' to designate reactions in which a specific antigen antibody response is involved or is considered probable Some confusion has existed with respect to the inability to demonstrate repeated or previous contact with the exciting agent (antigen) In these instances the similarity in clinical manifestations necessitate their inclusion among the allergic disorders

Bickerman, H A, Cohen, B
Subjects Stimulated
by Antitussive Agent
Ibid The Cough Response
Part II Evaluation
Boyd,
Ibid
Brown
Cass,

Ibid

Ibid
1958
Cass, L J, Frederik, W S, and Andosca, J B Quantitative Comparison of Dextromethorphan Hydrobromide and Codeine, Am J M Sc 227 291, 1954
Chakravarty, N K, Matallana, A, Jensen, R., and Borison, H L Central Effects of Antitussive Drugs on Cough and Respiration, J Pharmacol & Exper Therap 117 127, 1956
Denton, R
Douglass, B
Goodman, L New
York
Green, A F, and ... The Action of Analgesics and Nalorphine on the Cough Reflex
Hayes, E W,
Chro
Hobby A W
Konzett, H
67 3
May, ... flex by Pentobarbitone and

Phillips, ... ough Analysis of Etiologic
1956
Ratner, ... Clin North America 31

Tiffeneau, R La toux expérimentale Méthode de production Exposé analytique, Thérapie 11 265, 1956
Tuft L, and Levin, N M Studies of the Expectorant Action of Iodides, Am. J M Sc. 203 717, 1942
Van Dongen, K The Effect of Narcotine, Ticarda and Romilar on Coughs and on the Movements of the Cilia in the Air Passages, Acta physiol et pharmacol neerl 4 500, 1956
Winter C A, and Flataker, L Antitussive Compounds Testing Methods and Results, J Pharmacol & Exper Therap 112 99, 1954

Table 34 Clinical Allergic Disorders

A *Involving Multiple Systems* —
  1 *Serum sickness* Usually occurring 7 to 12 days after administration, injected or ingested, of a foreign serum or drug
  2 *Allergic or "anaphylactic" shock* Acute reactions to foreign substances to which patient has been previously sensitized, occurring within seconds or minutes
B *Involving the Respiratory System* —
  1 *Allergic rhinitis*
    (a) *Seasonal rhinitis* hay fever, pollinosis
    (b) Perennial rhinitis (vasomotor rhinitis)
  2 *Bronchial asthma*
    (a) Extrinsic inhalants, ingestants injectants
    (b) Infectious (so-called 'intrinsic') bacterial allergens, foci of infection
C *Involving the Gastrointestinal System* —
  1 *Acute* pylorospasm, nausea emesis, diarrhea, colicky pain
  2 *Subacute or chronic* spastic constipation, mucous colitis, pruritus ani perianal eczema
  3 *Henoch's purpura*
D [illegible] cosmetic [illegible]
  2 *Atopic dermatosis*
    (a) Eczematoid contactants and occasionally inhalants
    (b) Venenata contact dermatitis due to plants, vegetable sources, chemicals cosmetics and animal danders
    (c) Medicamentosa drug eruption due to individual idiosyncrasy or hypersensitivity
E *Involving the Blood and Vascular System* —
  1 Agranulocytosis drug and chemical hypersensitivity
  2 Erythroblastosis fetalis passive transfer of hemolytic antibodies (Rh) from maternal circulation to fetus
  3 Urticaria [illegible]
F [illegible]
  2 *Rheumatic fever*
  3 *Lupus erythematosus disseminatus*
  4 *Thromboangiitis*
  5 *Nonthrombocytopenic purpura*

PHYSIOLOGIC AND PHARMACOLOGIC CONSIDERATIONS

In order to assess the value of pharmacologic agents in the management of allergic disease, a brief review of some of the current concepts on pathogenesis appears to be desirable Both antigens and antibodies have been demonstrated by biochemical technique It has been found that most antigens consist mainly of protein, although polysaccharides and lipids in combination with carbohydrates can produce antibodies in mammals Landsteiner and others have shown that low molecular weight substances, such as drugs, often display antigenic activity In these instances it has been postulated that the drug or chemical compound acts as a hapten and becomes coupled with protein which is capable of inducing antibody formation Since it is commonly recognized that most living cells possess the ability to produce protein, it is theoretically possible for these cells to produce antibody when they come in contact with antigen and secure it Considerable recent

CLINICAL CONSIDERATIONS

The diseases of allergy comprise a group of heterogeneous disorders with both acute and chronic manifestations. The symptoms may vary from a mild urticaria or rhinitis to a severe anaphylactic reaction with fatal termination. It has been variously estimated that approximately 10 per cent of the population of the United States or between 16 and 17 million people, suffer from allergic disease which ranks third in prevalence among the chronic diseases in this country.

In classifying the disorders of allergy due to hypersensitivity the allergist for the most part has been guided by historical developments in the field of immunology in which the antigen antibody relationship has played a dominant role. While these concepts have been invaluable in the development of diagnostic procedures and specific management, i.e., using the suspected allergen in determining the cause as well as for treatment by hyposensitization nevertheless from the pharmacologic point of view which involves symptomatic management of these disorders the immunologic classification has generally proved cumbersome. Perhaps a simpler way to consider these disease entities especially from the viewpoint of drug therapy, is to group them anatomically with reference to a specific organ or tissue. Such a classification is illustrated in Table 34.

From the clinical viewpoint the allergic disorders involving the respiratory …stem are perhaps the most important representing over 50 per cent of the al…rgies encountered in the practice of medicine.

Although it is generally recognized that the tendency to develop sensitivities …ereditary, the exact genetic mechanism remains in doubt. The particular …rens to which a person predisposed by heredity will become sensitized depend…ly on environmental exposure. It appears likely that any protein which is …d or ingested may cause sensitivity, and the list of such active agents is …ntly expanding. Emphasis is scarcely required to point out that each new …t and miracle drug developed introduces the problem of iatrogenic disease … group of sensitized individuals.

…re are a number of allergic disorders, i.e., asthma, perennial rhinitis, and … in which extrinsic allergens cannot be regularly demonstrated. In some … there is an associated chronic infection particularly of the paranasal …nchi and tonsils. The causal relationship to infection is only infrequently … the relief of symptoms occurring after the medical or surgical eradica…h infection. The occurrence of upper respiratory viral infection is …ssociated with exacerbation of the allergic state, whereas pneumococcal …h fever are followed by lessening of the allergic state. There is a …ody of experimental evidence which suggests that bacterial sensitiza… factor in the pathogenesis of such disease states as rheumatic fever, …itis, periarteritis nodosa, acute lupus erythematosus, and perhaps …diseases. Hypersensitivity has generally been accepted as one aspect …esponse which serves to localize infection and protect the organism … of widespread dissemination. More recent studies by Rich and …doubt upon the protective nature of this hyperimmune response … form of hypersensitivity as the mechanism for the pathoge…ses mentioned above.

mental anaphylaxis and some of the clinical manifestations of allergy However the treatment of clinical anaphylaxis requires epinephrine and its alleviation by antihistamines has been questioned

PHARMACOLOGIC MANAGEMENT OF ALLERGIC DISORDERS

Basic knowledge has been accumulated over the past half century in the field of allergy however, advances in clinical management based upon this knowledge have only scratched the surface In reviewing the material presented above we have been impressed but not a little disappointed by the apparent difficulty in applying the strides made in the laboratory to the practical care of the allergic patient It is evident that much careful work remains for the inquiring physician

The application of allergic principles to clinical practice is based upon (1) removal of the offending allergen when such can be demonstrated (2) hyposensitization procedures with preparations of specific allergen and (3) symptomatic management Before undertaking treatment, diagnostic procedures including both the type of allergic disorder and the etiologic causation must be thoroughly investigated As with other disease syndromes, a complete history and physical examination are imperative since they often provide a clue to the offending substance or substances involved in the allergic reaction Skin tests may confirm the history or help in bringing to the attention of the patient and physician a forgotten bit of history Most clinicians now believe that when a discrepancy exists between the history and skin tests, the history is a more accurate diagnostic tool The history may indicate that the patient is sensitive to a given substance despite the fact that the skin test reaction is negative

If the allergic disorder can be traced to one or more antigen antibody reactions the prognosis for successful control by means of elimination or hyposensitization is frequently good Skin test reactions are usually multiple and are more frequently encountered in children than adults Food sensitization with test allergens is discovered more readily in children The use of elimination diets is required to determine the etiologic factor when the skin test is negative When the cause is undetermined major recourse must be made to the symptomatic management of the allergic manifestation

Environmental Control

If the allergic symptoms in the main are caused by contact with offending substances in the environment, the logical treatment is either removal of the patient from that environment or removal of the offending substance from the patient's vicinity Ingestant offenders may be controlled by eliminating them from the patient's diet When the offending allergen is an inhalant there are two avenues available for control by elimination The patient may temporarily take up residence in a pollen free area when seasonal pollinosis is implicated Depending upon the type of inhalant responsible another measure includes scrupulous attention to the maintenance of an atmosphere free from such substances as dusts molds feathers animal danders wools cottons and horsehair This is aided by mechanical devices such as air filters and room air conditioners equipped with an efficient

evidence supports the view that the plasma cell and lymphocyte are the maj source of antibody

The interaction between antigen and antibody results in certain pathophysio logic changes in various tissues and organs of the body In the main these involve smooth muscle blood vessels glands, and collagen The major pathologic changes which occur in these tissues are edema smooth muscle contraction, and hyper secretory activity of glands In asthma allergic rhinitis urticaria, and angioedema the basic response is local vasodilatation and increased capillary permeability lead ing to tissue edema in the mucosa of the respiratory tract, skin and subcutaneous tissues In addition spasm of the smooth muscle of the bronchial tree and the increased secretion of seromucinous material from the bronchial glands are re sponsible for the major pathologic changes It is not known whether the reaction between antigen and antibody takes place in the cells upon the surface of the cells or in the blood stream

There has been considerable speculation concerning the intermediary mecha nisms whereby the union of antigen and antibody results in the tissue changes de scribed above Since Dale's original studies with histamine and sensitized uterine muscle strips an enormous literature has accumulated concerning the chemical nature of an intermediate substance produced by the reaction of antigen and anti body which in turn causes the various phenomena observed in allergic disease It has been proposed that tissue alteration results from the release of such chemical substances as histamine heparin acetylcholine serotonin and possibly other chemi cal agents There is in fact no simple explanation for the chemical mediation of he allergic reaction In this respect Feldberg and Smith have advanced the eory that serotonin which is found abundantly in platelets and in the granules of e tissue mast cells both of which are present in large numbers in the respiratory e during the allergic reaction is responsible for the release of histamine from the s Because many of the allergic manifestations can be reproduced in non tized individuals or animals by histamine and can be partially or entirely sed by drugs with known antihistamine activity histamine or a histamine substance has been implicated as the intermediary in allergic reactions

he physiologic and pharmacologic activities of histamine are ubiquitous so e exact nature of its place in allergy remains in dispute It is beyond the f this chapter to review all the properties of histamine Perhaps the most ate summation was made by Dragstedt in 1915 The evidence for the tion of histamine in certain physiological and pathological reactions varies unded assumption and illogical inference to substantially concrete and proof

idence indicting histamine as responsible for anaphylaxis first proposed resulting from the liberation of histamine from an inert bound form injury is caused by the interaction of antigen and antibody has been d to other types of allergic manifestations. However Cooke has em attempts to demonstrate an excess of histamine in the blood of attacks of allergic disease have generally failed From the clinical aps the strongest evidence in favor of the histamine s the relative effectiveness of potent antihistam

determining the type of offending allergen by various skin testing procedures the techniques of hyposensitization are described in current textbooks of aller

Symptomatic Management With Pharmacologic Agents

Although specific measures of environmental control and hyposensitizat provide a rational basis for the therapy of allergic disorders, these measures do promptly eliminate symptoms in a considerable number of patients Expert syn tomatic management is therefore sought by the use of suitable pharmacolo agents Combined employment of specific therapy referred to above and adm tration of antiallergic drugs have often provided adequate control of many of distressing symptoms of allergy In the presence of such acute states as anaphyla and status asthma, drug therapy alone is at times lifesaving

The administration of suitable agents may restore to normal the pathophys logic disorders caused by allergic disease Because of the variations in response the different disease entities, the claim has often been made that the antispasmod expectorants, antihistaminics, and sedatives commonly used have no effect on course of the allergic process and in certain instances may be more disturbing th effectual Because of the inconsistent results achieved, many of these patients a denied a considerable measure of relief which could be provided by properly appl drug therapy The rationale of the use of substances in the prevention and treatme of allergic manifestations is as follows (1) relief of vasodilatation, mucosal eden and bronchospasm (2) facilitation of bronchial drainage, (3) inhibition of histami activity (4) sedation, (5) modification of tissue reactivity by corticotropin and t corticosteroids and (6) less well defined therapeutic objectives Many of the dru to be discussed provide relief by more than one mode of action Thus, vasoco strictors such as epinephrine are potent bronchodilators and the xanthine deriv tives, in addition to relaxing smooth muscle spasm have a pharmacologic effe on tissue edema

Relief of Vasodilatation, Mucosal Edema, and Bronchospasm—Althoug many therapeutic agents have been effective as vasoconstrictors and bronchodil tors, no single drug has proved entirely satisfactory Adverse side reactions, lac of sustained effect, and the development of tolerance have presented major stum bling blocks The judicious use of combinations of drugs, addition of sedative an antinausea factors, and alternate routes of administration have been helpful i overcoming some of these obstacles From a pharmacologic standpoint, the mor common drugs of this category are the sympathomimetics, anticholinergics, an the xanthine derivatives The principal drugs, together with their newer analogues in common use today will be discussed in this section

Adrenergic or Sympathomimetic Agents —Among the most effective drug in the treatment of allergic manifestations resulting from vasodilatation, mucosa edema, and bronchospasm are the sympathomimetics A list of these is illustrated in Table 35

Epinephrine Since its isolation at the turn of the century, this hormone of the adrenal medulla has been the most widely used agent in the symptomatic ment of the allergic state Its action includes constriction of the blood vessels

filter. Relief of the symptoms of hay fever or asthma caused by air borne inhalants is not complete since recent investigations into the efficacy of these devices have shown that many conventional room air conditioners remove only the larger pollens from the air. A combination of cloth filter and electronic precipitator is probably the best arrangement now available, especially when used continuously. Efficiency in the removal of pollen is increased when cooling units are used in conjunction with recirculation of air since much of the pollen will deposit upon the moist condensing coils, however, this may be accompanied by excessive cooling with continuous operation. The relief from these devices depends upon the habits of the patient and the amount of time spent in such a room. A filter in the room may be of considerable value to people who cannot use other measures. Environmental control of allergic disorders caused by the inhalants does not result in cure but may give considerable relief to individuals who remain in a pollen free area for extended periods. Complete restriction to a pollen free room, even in a hospital, has generally not met with patient acceptance (Novey and associates).

Hyposensitization

Although the exact mechanisms involved in hyposensitization remain obscure, the best evidence at present points to the formation of a circulating antibody, described by Cooke as the 'blocking antibody,' which is believed to prevent the union of antigen and its antibody. Gradually increasing doses of allergenic extracts injected at appropriate intervals produce an increased titer of the 'blocking' antibodies in the serum which then has the capacity to combine preferentially with the allergen and thus apparently prevent it from reacting with the sensitizing antibody. The basic principle in hyposensitization therapy is to increase the tolerance of the patient to the causative allergen. A review of the literature indicates that considerable variation exists in the exact degree of benefit conferred by hyposensitization. This appears to be due to the variable influence of the following factors (1) the demonstration of a reliable positive skin test, (2) the degree of hypersensitivity, (3) the type of allergic disorder, (4) the age of the patient, (5) predisposing environmental factors such as dust, humidity, and temperature, (6) chronic or intercurrent infection and (7) emotional trauma.

Although specific hyposensitization therapy is time consuming and often trying for the patient, it maintains its position as the most effective method of treatment in certain disorders such as hay fever. Similarly in seasonal asthma, where identification of the causative agent has been achieved the results have been successful in the majority of cases. On the other hand, injection therapy is generally unsuccessful in cases of nonseasonal asthma in which identification of the causative allergen has not been possible. In patients in whom multiple allergies exist, hyposensitization with a single offending allergen will have little or no effect upon the symptoms of the disease. Lowell has re emphasized the fact that "the correct selection of these (allergenic extracts) is of immense importance and this step is unquestionably best undertaken by one who has had considerable experience. Indiscriminate administration of allergenic extracts leads not only to failure but also to an understandable reluctance among many critical physicians to subject their patients to this rather expensive and time consuming procedure." The details of

Parenteral epinephrine (1 1 000) is the most useful drug in acute allergic emergencies such as anaphylactic shock and angioedema of the larynx, in which it may be given intravenously in doses of 0 3 to 0 4 ml for rapid effect In the treatment of asthma, injection of more than 0 3 ml subcutaneously is rarely necessary, with larger doses caution must be observed *in the presence of coronary artery disease* hypertension and hyperthyroidism Larger doses are attended by a higher incidence of toxic reactions involving the cardiovascular and central nervous systems Tremor, excitability, palpitation abnormal cardiac rhythms and occasionally a shocklike state are among the side effects encountered with larger or too frequently repeated doses

Self medication by hypodermic injections is not recommended for routine use since patients in an effort to obtain sustained relief, often overtreat themselves resulting in the rapid development of a refractory state Tolerance to Bronkephrine is reported as developing less frequently and to a lesser degree than with epinephrine A recent study by Blumenthal and his co-workers suggests that epinephrine fastness or refractoriness may be influenced by changes in the blood pH

The deposition of a fine bronchodilator mist on the mucosa of the bronchi and bronchioles of the respiratory tract presents many significant advantages over the parenteral use of epinephrine *Since the topical effect predominates* with relatively little activity resulting from systemic absorption, toxic effects in the therapeutic dosage range are minimal The ease of administration and its ready availability affords the patient with bronchospastic disease a measure of security not obtainable with injection therapy However, as with parenteral administration excessive use leads to increasing tolerance which can be overcome *in some instances* by the substitution of other sympathomimetic aerosols and by brief periods of withdrawal

As little as 0 1 ml of 1 100 epinephrine, 2 25 per cent racemic epinephrine (Vaponefrin) or 2 5 per cent racemic epinephrine with 0 5 per cent atrop ne sulfate (Dylephrin) nebulized by 4 to 6 compressions of the hand bulb of a Vaponefrin or De Vilbis #40 nebulizer may abort or relieve a mild bronchospastic attack within a few minutes The relief however, may be only temporary, and Richards and Barach have demonstrated that prolonged inhalations of dilute aerosols of epinephrine and phenylephrine (Neo-Synephrine HCl) over a period of 20 to 30 minutes 3 or 4 times daily, provided more effective bronchodilatation and bronchovasoconstriction in intractable bronchospastic states Diglio and Munch reviewed the reports of other investigators on the long term use of pressor aerosols and conducted a study in patients with hypertension, cardiac disease thyrotoxicosis and diabetes They found no untoward effects following the inhalation of many times the therapeutic doses of epinephrine Improper use of the aerosol may cause excessive dryness of the pharynx, and swallowing of the aerosol solution may cause epigastric pain

Isoproterenol Substituting an isopropyl group on the nitrogen in place of the methyl group *in the epinephrine formula* appears to increase the bronchodilating and vasodilating effects with a lowering of the pressor effect This compound isoproterenol is a valuable addition to epinephrine in the aerosol therapy of bronchial asthma Although its acute toxicity appears to be less than epinephrine

Table 35 Adrenergic Agents Employed in Allergic Disease

Generic Name	*Trade Name*	*Route of Administration*	*Usual Adult Dose*
Epinephrine (levo)	Adrenalin, Suprarenin	Parenteral (1:1000) Ophthalmic (1:1000) Aerosol (1.0%)	0.2-0.3 ml
(racemic)	Vaponefrin, Dylephrin*	Aerosol (2.25%)	0.2-0.5 ml
Ethylnorepinephrine	Bronkephrine, Butanefrine	Parenteral (1:500)	0.5 ml
Isoproterenol	Isuprel, Norisodrine	Sublingual Aerosol (0.5-1.0%)	5.0-10.0 mg 0.2-0.5 ml
	Aludrine, Aerolone Cpd., Nebu Prel	Aerosol (0.5%)	0.2-0.5 ml
Congeners Isoprophenamine		Oral	20 mg
α Protocatechyl Alc	Caytine	Oral Aerosol (0.5-1.0%)	2.0 mg 0.2-0.5 ml
Ephedrine (levo)	Efedron, Ephetonin	Oral Nasal Solution (0.5-2.0%)	15.0-50.0 mg 0.2 ml
	Ionephrin	Oral	15.0-50.0 mg
(racemic)	Racephedrine	Oral	25.0 mg
Congeners Methoxyphenamine	Orthoxine	Oral	50.0-200.0 mg
Etheylephedrine	Nethamine	Oral	25.0-50.0 mg
Phenylephrine	Neo Synephrine	Nasal Solution (0.25-1.0%) Aerosol (1.0%) Ophthalmic (0.12%)	0.1-0.2 ml 0.5-1.0 ml 0.1 ml
Phenylpropanolamine	Propadrine	Nasal Jelly (0.66%) Nasal Solution (1.0-3.0%)	0.2 ml
Naphazoline	Privine	Nasal Solution (0.1-0.05%) Ophthalmic Solution (0.1%)	0.1 ml 0.1 ml
Tetrahydrozoline	Tyzine	Nasal Solution (0.1-0.05%)	0.1-0.2 ml

*With atropine

and diminution of exudation of fluids in the tissue responsible for the particular allergic symptoms, and, probably more important than these properties, a potent bronchodilator effect. Experimental evidence indicates that epinephrine acts directly on the smooth muscle of bronchi and bronchioles to relieve bronchoconstriction. There are two routes of administration, parenteral and by inhalation as an aerosol. Onset of activity is rapid by either method usually within minutes, but the effects are transient for the most part, and frequent administration is therefo necessary to maintain relief of symptoms. To overcome this limitati parenteral use of epinephrine, slow release preparations, such as Ad and aqueous epinephrine suspension (Sus-Phrine) have been employed.

phedrine therapy in the older patient with prostatism It should be used cau iously, in small doses (15 mg) with aminophylline, in the presence of hyperten ion and coronary artery disease The maximum bronchodilator effect is usually eached within one hour after ingestion and persists for a period of approximately hours Increased duration of bronchodilator activity has been obtained with a ustained release preparation containing 50 mg of ephedrine combined with an on exchange resin (Ionephrin) In a preliminary study, clinical benefit has been aintained for approximately 6 to 8 hours following administration The incidence f side effects does not appear to be any greater than with smaller doses of the onventional ephedrine preparation

If ephedrine is given 3 or more times daily, its effectiveness often begins to ecline after several weeks because of the development of tolerance Increasing the ose may sustain the antispasmodic effect for a time, complete withdrawal for a eriod of 4 days or more frequently enables the patient to regain his former sponsiveness to this drug If the side effects of ephedrine prove troublesome nthetic amines chemically related to ephedrine, such as Racephedrine, ethyl phedrine (Nethamine), isoephedrine (Pseudoephedrine) and methoxyphenamine Orthoxine), may be substituted These preparations produce a similar but less ffective bronchodilator response milligram for milligram Except for isolated stances it is questionable whether or not they offer any real advantages over phedrine

The nasal solution of ephedrine is essentially a local vasoconstrictor with de ongestant properties and its pharmacologic effects are similar to the vasocon rictor agents to be discussed below

Phenylephrine, Phenylpropanolamine, Naphazoline, and Tetrahydro oline hese members of the sympathomimetic group are effective vasoconstrictors whose ain usefulness in the treatment of allergy pertains to their topical decongestant tion upon the mucous membranes of the upper respiratory tract and the con inctiva Although effective in the temporary relief of nasal congestion and ohthalmic symptoms all of these preparations to a greater or lesser degree result rebound vasocongestion and should not be continuously used in chronic allergic ates of the upper respiratory tract In this connection naphazoline (Privine) has en reported as perpetuating chronic rhinitis with prolonged use Another side fect of naphazoline shared by tetrahydrozoline (Tyzine) is the occurrence of dation particularly in infants and children In fact excessive dosages may cause vere drowsiness accompanied by profuse sweating Coma and shock have been ported in young children after overdosage or improper administration of a 0 1 r cent solution of Tyzine For children under 6 years of age 1 to 3 drops of a 05 per cent solution has been recommended at intervals of not less than 4 to 6 ours Since all of the agents of this group are pressor drugs it has been cus mary to urge caution when applied to patients with hypertension or hyperthy idism In addition to their use as topical vasoconstrictors phenylephrine and enylpropanolamine have provided moderate relief of bronchospasm and edema the bronchial mucosa when employed as aerosols in combination with epineph ne or isoproterenol

clinical experience indicates that side reactions, principally tachycardia, are often more marked than those of epinephrine Because of its effect of lowering blood pressure and peripheral resistance, its use may be preferred in patients with an associated hypertension, but increased excitability may outweigh these advantages Sublingual tablets containing 10 mg of isoproterenol, and an inhalant powder are available However, occasional depression of the T waves on the electrocardiogram has been observed following their use Clinical effectiveness of these routes of administration has been more erratic than with aerosol inhalation, and the incidence of adverse reactions with adequate doses has been considerably higher, averaging about 30 per cent These consisted of nervousness, tremor, dizziness, palpitation precordial pain nausea and vomiting

The most effective, as well as the safest method of administration clinically appears to be by aerosol inhalation in doses of 0 1 to 0 5 ml of the 1 200 dilution With this route of administration only a small percentage of patients experience toxic effects Pharmacologic activity of isoproterenol develops rapidly, usually within several minutes following inhalation Clinical experience has indicated that it may continue to exert bronchodilator activity in patients who have become refractory to epinephrine This compound has recently stimulated intensive research for chemical analogues possessing potent bronchodilator activity with minimal adverse effects The addition of phenylephrine, as in Nebu Prel (isoproterenol 0 4 per cent phenylephrine, 2 per cent) ameliorates some of the adverse cardiovascular effects such as the tachycardia and hypotensive reactions

Among newer congeners of isoproterenol undergoing clinical trial isopropheniamine and protocatechyl alcohol (Caytine) show considerable promise In common with the parent compound these preparations are potent bronchodilators whose main advantage appears to be their effectiveness by oral administration as well as by inhalation Onset of relief of asthma takes place approximately 30 minutes after ingestion but incidence of side effects is variable In general, reactions appear to be less than with sublingual isoproterenol When used as an aerosol, reactions to Caytine were rare in a large series of cases studied in our clinic In some patients with moderate asthma the degree of relief afforded by 20 mg of isopropheniamine frequently approached that of parenteral epinephrine, and when this oral preparation was combined with a tranquilizer or a mild sedative the severity of sympathomimetic stimulation was reduced

Ephedrine Either alone or in combination with theophylline, ephedrine is the most frequently employed oral medication for the relief of allergic symptoms especially the bronchospasm of asthmatic patients In the usual dose of 15 to 25 mg administered 2 or 3 times daily, it generally provides effective relief of a mild attack At this dosage level its administration also appears to have a prophylactic value The British advocate ephedrine as the preferred antispasmodic for routine use The dosage employed however is much greater than that commonly used in this country 50 mg at the beginning to 100 mg later on in treatment Doses as high as 200 to 300 mg were reported by Herxheimer as being well tolerated with a low incidence of side reactions In our experience, however, doses in excess of 50 mg are accompanied by an increased incidence of side effects including palpitation excitation, and insomnia Acute urinary retention is a distressing complication of

orded effective relief of obstructive dyspnea in selected patients In hay fever, ennial rhinitis and coryza, the anticholinergic drugs inhibit excessive nasal and rimal secretions, thus affording symptomatic relief In fact, many proprietary ld remedies" contain atropine or one of the other belladonna alkaloids These aloids as well as antihistaminic agents have, to a major degree, the disadvantage excessive drying of the mucous membrane of the laryngobronchial tree as well the nose, on continued use None is recommended for maintenance therapy for t reason

Untoward Reactions Adverse side effects of the anticholinergic drugs are on whole rather unpredictable For example, the dosage level of atropine required effective bronchorelaxation may exceed that ordinarily considered safe, the thetic congeners mentioned above were accompanied by mild side effects for most part These included dryness of the mouth and oropharynx, occasional rring of vision dizziness and, in some instances, urinary retention The anti linergic drugs are of course contraindicated in the presence of glaucoma Since e agents have a tendency to depress bronchial secretions, they are not suitable continued use and should be employed with caution in patients with retained etions who appear to have difficulty in raising thick, tenacious sputum The t' asthmatic with bronchorrhea may be benefited temporarily by this drying on

XANTHINE DERIVATIVES —The effectiveness of the xanthines in the treatment bronchial asthma is based on their ability to relax the smooth muscle of the heobronchial tree and reduce edema of the bronchial mucosa The most active nber of this group is theophylline and its various salts A list of these prepara s, together with some of the more common ephedrine combinations, is given in le 37

Since the report of Herrmann and Aynesworth in 1937, the administration of nophylline has become recognized as a valuable procedure for the relief of in table bronchospasm Bronchial asthma refractory to epinephrine frequently onds favorably to theophylline and its derivatives Acute paroxysmal dyspnea ciated with cardiac failure responds to theophylline not only because of bron l dilatation, but also because of its potent diuretic action All preparations heophylline are to some degree irritating to the gastric mucosa, this side effect n makes it difficult to administer the full therapeutic dose orally without the of measures designed to decrease gastric intolerance The effective use of nophylline in a program of asthma therapy has often been neglected in spite he well documented evidence concerning its effective bronchodilator activity

Patients with severe obstructive dyspnea who are refractory to the adrenergic pounds frequently obtain marked relief following the intravenous administra of 0 25 Gm aminophylline in 10 ml of diluent This injection should be per- ned slowly over a period of 8 minutes and may be repeated in 15 to 30 min

Rapid administration has been accompanied by severe reactions and in some nces death More prolonged bronchial relaxation in patients with severe dis can be accomplished by the infusion of 200 to 500 ml of 5 per cent dextrose istilled water containing 0 5 Gm aminophylline The first 100 ml should be inistered rapidly so as to obtain a high initial blood level and the remainder

Anticholinergic Agents.—Since one of the mechanisms postulated to mediate the smooth muscle spasm of bronchial asthma is the release of acetylcholine produced by stimulation of the parasympathetic nervous system, blockade of these bronchoconstrictor stimuli by anticholinergic agents would appear to offer a pharmacologic approach to the effective relief of this type of bronchospastic state. In theory, atropine and its congeners should be effective not only because of its bronchodilating action but also because it suppresses excessive secretions from the bronchial glands. A list of the more common members of this group is illustrated in Table 36.

Table 36. Anticholinergic Agents Used in Allergic Disease

Generic Name	Trade Name	Route of Administration	Usual Adult Dose
Atropine		Oral Subcutaneous Aerosol (0.5%)	0.4-0.6 mg 0.4-0.6 mg 0.2-0.5 ml
Scopolamine (Hyoscine)		Oral Parenteral	0.5 mg 0.5 mg
Methantheline	Banthine	Oral Parenteral	50 mg 50 mg
Epoxytropine tropate methylbromide	Pamine	Oral Aerosol	2.5 mg
Oxyphenonium	Antrenyl	Oral Aerosol (0.05%) Intravenous	5 mg 1 ml 1 mg
Diphemanil	Prantal	Oral Parenteral	100 mg 35-50 mg

Among the earlier symptomatic remedies for the treatment of asthma has been the inhalation of smoke from the burning of stramonium in the form of various powders and 'asthma' cigarettes. Occasional individuals were benefited and relief when it did occur was due largely to coughing and expectoration of retained secretions. This form of therapy has been generally abandoned. Of the naturally occurring belladonna alkaloids, atropine, while it produces relaxation of the smooth muscles of bronchi and bronchioles, is a considerably less potent bronchial antispasmodic in the conventional dosage recommended than drugs of the adrenergic group. In general, the clinical results obtained with these anticholinergics in acute episodes of asthma have been erratic and disappointing. Their chief usefulness has been limited to combinations with drugs of the adrenergic or xanthine groups to help diminish the frequency and severity of attacks. Aerosol preparations of this type include Dylephrin and Aerolone Compound.

Clinical reports have attested to the value of several synthetic anticholinergic preparations in the treatment of bronchospasm. Methantheline (Banthine) in doses of 50 m[illegible] creases in vital capacity [illegible] tomatic improvement of [illegible] reported with aerosols of epoxytropine tropate (Pamine) and oxyphenonium (Antrenyl). In our clinic, 35 to 50 mg. of diphemanil (Prantal) intramuscularly

Untoward Effects The most troublesome side effect of oral aminophylline is the high incidence of gastric intolerance, nausea and vomiting often limits the administration of effective therapeutic amounts of this drug Enteric coated aminophylline although materially reducing the incidence of these side reactions results in impaired absorption with blood levels about 10 per cent of those required for bronchodilatation It is therefore useless In attempting to mitigate gastrointestinal intolerance to oral aminophylline and not interfere with absorption it has been combined with various antinausea preparations For example, Aminodrox contains aluminum hydroxide gel, in Cardalin and the Dainite tablets aminophylline is combined with 160 mg of aluminum hydroxide and 30 mg of ethyl aminobenzoate. Patients are able to tolerate 300 mg of aminophylline in these combinations with relatively few side effects These antinausea factors do not impair absorption since blood levels of theophylline following oral ingestion of 300 and 600 mg of Cardalin were almost as good as those obtained after the intravenous or rectal administration of comparable doses of aminophylline

A 20 per cent alcoholic solution of theophylline (Elixophyllin) has been studied in our clinic With an average dose of 45 ml in the midafternoon and 60 ml on retiring approximately 85 per cent of 149 patients obtained moderate to excellent relief of obstructive dyspnea and wheezing In general side reactions were mild and only 3 patients found them severe enough to warrant discontinuance of medication Ventilatory function studies following a single dose of 60 ml of Elixophyllin equivalent to 400 mg of aminophylline showed significant increases in vital capacity and midexpiratory flow rates The efficacy of this preparation in the relief of bronchospasm may be attributed to (1) more rapid absorption of theophylline, possibly because of its facilitation by the alcohol and of the fact that a liquid preparation is more readily available than a compressed tablet for absorption from the upper gastrointestinal tract and (2) the relaxing effect of alcohol itself in the tense anxious patient

In an effort to augment therapeutic effectiveness by permitting higher dose levels orally, several new salts of theophylline have been made which are reported to cause less gastric irritation and a more rapid rate of absorption than aminophylline Among the preparations available for clinical use are choline theophyllinate (Choledyl) theophylline methylglucamine, and theophylline sodium glycinate The clinical value of these newer salts above that of aminophylline combined with antinausea factors has not been demonstrated satisfactorily In fact the present coating on Choledyl although it removes the odor delays absorption

The long term daily use of aminophylline prophylactically may in some instances result in a cumulative effect with an increase in adverse side reactions as well as the development of refractoriness This can be prevented by a program of intermittent therapy in which ephedrine is substituted for aminophylline for periods of a week or more A number of reports have stressed the dangers of aminophylline therapy in children In addition to severe side reactions including acidosis delirium hyperpyrexia, convulsions and coma, a number of deaths have occurred in children under 4 years of age who were given rectal suppositories ...ng 0.25 Gm or more of aminophylline In this connection it must be

Table 37 Salts of Theophylline and the More Common L
Ephedrine Employed in Bronchial Asth

Generic Name	*Trade Name*	*Route of Administrat*
Theophylline		Oral
	Elixophyllin	Oral
Aminophylline		Oral Intravenous Intramuscu Rectal
Theophylline Monoethanolamine	Theamin, Clysmathane	Rectal
Choline Theophyllinate	Choledyl	Oral
Theophylline Methylglucamine	Glucophylline	Oral Parenteral Rectal
Theophylline Sodium Glycinate	Glytheonate	Oral Rectal
	Theoglycinate	Oral Rectal
Ephedrine combinations with varying salts of Theophylline	Amasec Cholarace Dainite Luasmin Nephenalin Quadrinal Tedral	Oral Oral Oral Oral Oral Oral Oral

infused over a period of 1 to 2 hours This may be repe
3 successive days in order to terminate a severe attack

The rectal instillation of 0.6 Gm dissolved in 30 ml
effective relief without the danger of serious cardiovascu
tion this method has the advantage of offering the patier
administration which can be performed by a member of th
F catheter and 30 ml syringe A disposable [illegible] al unit
[illegible] plastic s
[illegible] Amin
[illegible] has produced variable results This er
spastic states probably results from variations in absorpti
ministration of aminophylline is exceedingly irritating and
pain which is only partially mitigated by the addition of 1 m
to the injection

For prophylactic therapy and the relief of mild to mo
chospasm, administration of aminophylline by mouth on
[illegible]

Untoward Effects The most troublesome side effect of oral aminophylline the high incidence of gastric intolerance, nausea and vomiting often limits the ministration of effective therapeutic amounts of this drug Enteric coated amino ylline, although materially reducing the incidence of these side reactions, results impaired absorption, with blood levels about 10 per cent of those required for onchodilatation It is therefore useless In attempting to mitigate gastroin tinal intolerance to oral aminophylline and not interfere with absorption, it has n combined with various antinausea preparations For example, Aminodrox ntains aluminum hydroxide gel, in Cardalin and the Dainite tablets, amino ylline is combined with 160 mg of aluminum hydroxide and 30 mg of ethyl inobenzoate Patients are able to tolerate 300 mg of aminophylline in these nbinations with relatively few side effects These antinausea factors do not pair absorption since blood levels of theophylline following oral ingestion of 300 d 600 mg of Cardalin were almost as good as those obtained after the intra ious or rectal administration of comparable doses of aminophylline

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3 mg per pound of body weight and should not be given more often than twice in a 24 hour period. In children under 4 years of age, special precautions should be observed regarding hydration and the avoidance of acidosis.

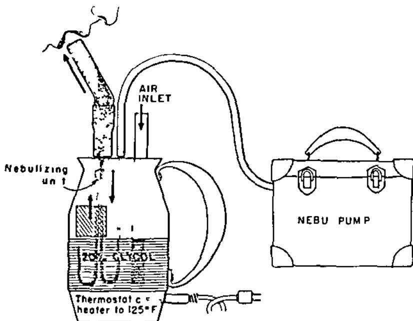
Although descriptions of mixtures and combinations of drugs have been avoided in this chapter for the most part, it should be emphasized that many of the more popular remedies for the treatment of asthma contain ephedrine in combination with various salts of theophylline. The major usefulness of these oral preparations consist in their ability to control minor attacks of asthma and to lessen the frequency of such attacks. There are a number of reports which would indicate that the addition of ephedrine to theophylline potentiates bronchodilator activity with a corresponding increase in toxicity however. The administration of aminophylline by aerosol or powder insufflation is clinically ineffective and may intensify bronchospasm due to local irritation.

Facilitation of Bronchial Drainage.—In addition to bronchospasm, retention of bronchial secretion is frequently operative in the production and maintenance of partial bronchial obstruction. An excessive production of mucus often occurs as a result of an allergic response to inhaled allergens, irritation of an edematous bronchial mucosa, chronic bronchial infection or unknown factors. The presence of these retained secretions provokes paroxysms of coughing and accentuates spasm of the tracheobronchial tree. Certain physiologic mechanisms for the removal of these secretions such as the ciliary action of the lining epithelium are frequently impaired. The consequences of bronchial obstruction by retained secretions are serious as to warrant every effort both pharmacologic and mechanical to facilitate bronchial drainage. The following section deals with pharmacologic therapy as expectorants and aerosols which aid the elimination of retained secretions.

EXPECTORANTS.—These drugs assist in the removal of mucus or exudate from tracheobronchial passageways. Tuft and Levin describe two mechanisms of (1) secretolysis—liquefaction of the bronchial secretions, thereby making sputum more fluid and less viscid and (2) excretomotor—stimulation of the muscle of the bronchi to increase peristaltoid activity. Liquefaction is about by the actual secretion or excretion of the expectorant agent into bronchial secretions with a lowering of the viscosity so that it becomes less ... The cough mechanism may be more effective after the use of expec... in clearing the upper bronchial passages of secretions. The oral prepara... known as "expectorants," which serve to increase the respiratory tract fluid ... the bronchial secretions less viscid have been described in detail in ...8 The Choice of Antitussive Agents. The two preparations which have ...ost effective in the treatment of bronchial asthma are the iodides in ...lts and organic compounds), and syrup of ipecac. In addition glyceryl ..., in the form of Robitussin appears to be at times a moderately effec...torant agent in asthmatic children.

...L THERAPY.—Three types of aerosols have been used to help liquefy ...ucoid or mucopurulent material. They have been classified as humidi...ant, and mucolytic. ...ication has been considered helpful in the treatment of certain patients ...d chronic respiratory disease. This is particularly true in those sec-

of the country where colder weather means spending the major portion of ay in an artificially heated room A combination of excessive dryness and dust has accumulated about steam radiators or in hot air ducts *appears at times* rpetuate symptoms of obstructive dyspnea in patients with asthma The the steam kettle was a relatively ineffective method of attempting to cor ie low humidity



g 24—Adequate humidification is provided by a superheated nebulizer wh ch del vers nately 3 5 ml per m nute of aerosol m st thermostatically controlled to mainta n a ture of 120 to 125° F

ie inhalation of a mist produced by the nebulization of normal saline solu ay be helpful 2 to 10 ml is nebulized by the mouth rebreathing bag tech or into a plastic face tent by means of a small pump or oxygen at a flow ers per minute 4 times daily The Vaponefrin or De Vilbis #40 nebulizer provides a small particle size mist ranging between 2 to 3 microns in mean is employed Within the past 2 years a more efficient method has been in our clinic which provides for the inhalation of a saline or 10 per cent ne glycol aerosol heated to 120 to 125° F This is accomplished by means rmostatically controlled high flow nebulizer, illustrated in Fig 24 capable olizing 3 5 ml of solution per minute The wide range of particle size re deposition along the entire tracheobronchial tree In addition consider ainout of water vapor occurs when the heated aerosol comes in contact e relatively cooler mucous membranes of the respiratory tract Clinical demonstrated increased ease in the expectoration of inspissated plugs of and retained secretions from the lower respiratory tract as demonstrated by c studies of the recovered material

e rationale for the use of detergent or 'wetting agents is based on their

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Although descriptions of mixtures and combinations of drugs have been avoided in this chapter for the most part, it should be emphasized that many of the more popular remedies for the treatment of asthma contain ephedrine in combination with various salts of theophylline The major usefulness of these oral preparations consist in their ability to control minor attacks of asthma and to lessen the frequency of such attacks There are a number of reports which would indicate that the addition of ephedrine to theophylline potentiates bronchodilator activity with a corresponding increase in toxicity, however The administration of aminophylline by aerosol or powder insufflation is clinically ineffective and may intensify bronchospasm due to local irritation

Facilitation of Bronchial Drainage —In addition to bronchospasm retention of bronchial secretion is frequently operative in the production and maintenance of partial bronchial obstruction An excessive production of mucus often occurs as a result of an allergic response to inhaled allergens, irritation of an edematous bronchial mucosa, chronic bronchial infection, or unknown factors The presence of these retained secretions provokes paroxysms of coughing and accentuates spasm of the tracheobronchial tree Certain physiologic mechanisms for the removal of these secretions, such as the ciliary action of the lining epithelium are frequently impaired The consequences of bronchial obstruction by retained secretions are so serious as to warrant every effort, both pharmacologic and mechanical, to facilitate bronchial drainage The following section deals with pharmacologic therapy, such as expectorants and aerosols which aid the elimination of retained secretions

Expectorants —These drugs assist in the removal of mucus or exudate from the tracheobronchial passageways Tuft and Levin describe two mechanisms of action (1) secretolysis—liquefaction of the bronchial secretions, thereby making the sputum more fluid and less viscid, and (2) excretomotor—stimulation of the smooth muscle of the bronchi to increase peristaltoid activity Liquefaction is brought about by the actual secretion or excretion of the expectorant agent into the bronchial secretions with a lowering of the viscosity so that it becomes less tenacious The cough mechanism may be more effective after the use of expectorants in clearing the upper bronchial passages of secretions The oral preparations known as "expectorants," which serve to increase the respiratory tract fluid and render the bronchial secretions less viscid, have been described in detail in Chapter 28, The Choice of Antitussive Agents The two preparations which have proved most effective in the treatment of bronchial asthma are the iodides (inorganic salts and organic compounds), and syrup of ipecac. In addition, glyceryl guaiacolate, in the form of Robitussin, appears to be at times a moderately effective "expectorant" agent in asthmatic children

Aerosol Therapy —Three types of aerosols have been used to help liquefy tenacious mucoid or mucopurulent material They have been classified as humidifying, detergent, and mucolytic

Humidification has been considered helpful in the treatment of certain patients with acute and chronic respiratory disease This is particularly true in those sec-

ether anesthesia is occasionally lifesaving in status asthma where air flow is sly impeded by retained secretions The indication for this measure is far ommon in our experience as a result of the use of steroids, and mechanically ed cough

nhibition of Histamine Activity —The theoretical rationale for the use of his e antagonists, or 'blocking agents,' in modifying or preventing allergic mani ions has been discussed in the previous section Their chief action involves etition with released histamine or 'H substance at its site of action, pre ig its effect on the receptor cells Since the demonstration by Bovet and in 1937 that certain phenolic ethers possess antihistaminic activity, literally eds of drugs of this group have been synthesized To add to the confusion, ethora of drugs introduced into clinical practice in the past decade has yielded oints of discrimination between them either in terms of effectiveness or de of toxicity ' Perhaps in no other class of therapeutic agents does the physician a wider choice of preparations, but in no other group of drugs does a dis ig choice offer less reward"

is with many other palliative pharmacologic agents, the clinical evaluation tihistamine therapy depends on the therapeutic benefit derived as opposed adverse side reactions The antihistamine of choice, therefore, would be one which is most effective with the fewest side reactions Since this may for each individual many physicians have resorted to the empiric use of a er of antihistaminic drugs for each patient in order to select the most effec ne It should be emphasized that recourse to several different drugs of this at varying dosage levels should be made before concluding that antihis ics are ineffective in any given individual

ince the organic structure and pharmacologic activity of the antihistaminics similar there has been little attempt to classify these agents other than to out individual preparations which may depart somewhat from the pattern group Brown has divided the antihistamines into 3 main groups based their toxic side reactions

Group I—These are least potent and least reactive Antistine, Neohetra mine Thephorin

Group II—These are moderately potent and moderately reactive Pyri benzamine, Chlor Trimeton, Trimeton, Diatrine, Perazil, Histadyl Neo Antergan, Tagathen, Ambodryl and Clistin

Group III—These are highly potent but also highly sedative Benadryl, Decapryn and Phenergan

he antihistamines have found wide usage in the symptomatic therapy of a y of allergic states Although varying degrees of clinical benefit are evident h conditions as hay fever, perennial vasomotor rhinitis urticaria serum sick and perhaps anaphylactic like states these agents have been disappointing treatment of bronchial asthma Best results are achieved in patients with al hay fever, or urticaria In hay fever relief is often more apparent in the edematous phase when itching, sneezing and rhinorrhea are pronounced on, when nasal obstruction becomes more prominent, the antihistamines

ability to lower viscosity of sputum Numerous investigators have pointed out that the local deposition of wetting agents will reduce surface tension and loosen retained mucus secretions from the mucosa by their emulsifying action Agents such as alcohol glycerin and Zephiran chloride have been used by aerosol as vehicles for antibacterial or antispasmodic drugs for some time Following the enthusiastic report by Miller and his associates on the use of a nontoxic detergent superinone in the aerosol preparation Alevaire an extensive and controversial literature has accumulated Preliminary studies with Alevaire aerosol in our clinic showed that this material was at times irritating to the respiratory tract and other investigators have remarked on the irritant nature of Alevaire suggesting that the alkaline pH in excess of 8 5 was responsible

Levine reported a study on 96 patients with bronchopulmonary disease complicated by bronchospasm or bronchial obstruction many of whom were apparently benefited by a new detergent aerosol which contains potassium iodide as a mucolytic chemical This aerosol Tergemist has the following composition 0 125 per cent of the detergent Tergitol 08 and 0 1 per cent potassium iodide in sterile water The total daily dose ranged between 12 and 25 ml administered in four 30 minute periods of inhalation No irritation or toxicity was noted

However there are no convincing well controlled studies which adequately confirm the value of these detergents In our studies detergents did not enhance the absorption of penicillin aerosol as might have been expected if surface tension of retained secretions were lowered The therapeutic efficacy reported may depend wholly or in part on other measures i e the addition of bronchodilator and antibiotic agents administered in conjunction with these aerosols and the obvious benefit of humidification accompanying such aerosol therapy

Following the initial optimistic reports concerning the effectiveness of mucolytic or proteolytic enzymes such as trypsin and pancreatic desoxyribonuclease in digesting and thinning out the bronchial secretions in chronic pulmonary disease recent studies have more clearly defined the indications for the use of enzyme therapy and stressed the hazards of such therapy It has become evident that little or no benefit is obtained in bronchial asthma the liquefaction of sputum with facilitation of bronchial drainage in this allergic disease is at best only temporary Our experiences with Tryptar (crystalline trypsin) and pancreatic dornase (pancreatic desoxyribonuclease) have not been encouraging Using the recommended dose of 125 000 units of Tryptar dissolved in 3 ml of Sorenson's buffer twice daily irritation with pharyngitis and glossitis became apparent in a considerable number of patients by the third or fourth day of treatment with bronchospasm precipitated by the aerosol itself Less irritation took place after the inhalation of *pancreatic dornase, but the degree of benefit we observed* was not worth the trouble In addition to local irritative phenomena marked allergic reactions may occur since enzymes derived from nonhuman sources are capable of exciting antibody production in hypersensitive individuals Considerable speculation has arisen concerning the late toxic effects of these enzymes on the epithelium of the bronchial mucosa, described by Farber as atypical metaplasia

While it is not the purpose of this chapter to discuss physical or mechanical measures for aiding bronchial drainage, the use of bronchoscopic aspiration under

Benadryl and Phenergan, may offer a special advantage, particularly *in the short* term therapy of severe pruritus and 'night cough" where the antihistaminic effect is augmented by much needed sedation

Table 38 Selected Antihistaminic Agents Employed in the Treatment of Allergic Diseases

Trade Name	*Remarks*	*Usual Adult Dose*
Antistine	Therapeutic action weaker than most of the other antihistamines, less irritating, 20% of patients *exhibit side reactions such as nausea and drowsiness*	*100 mg q i d* (Nasal 0 5% Sol n)
Benadryl	Has moderate antispasmodic action, produces high incidence of sedation	50 mg t i d (Parenteral 10 mg)
Chlor Trimeton	Good therapeutic efficacy *with low incidence of side effects*	2-4 mg q i d (Parenteral 5 20 mg)
Clistin	Potent with low incidence of side effects, exhibits weak atropine like anticholinergic activity	4 mg t i d
Decapryn	[illegible]	12 5 mg t i d
Diatrine	[illegible]	50 *mg* q i d
Dimetane	[illegible] reactions	2 4 mg t i d
Histadyl	Incidence of sedation low	50 100 mg t i d or q i d
Neo Antergan	Incidence of sedation, low	25 50 mg t i d
Neohetramine	*Requires larger dosages but side effects are less* sedation less frequent	50 100 *mg q i d*
Perazil	Prolonged action and low incidence of toxic effects	50 mg b i d
Phenergan	Longer duration of action, usefulness in asthma limited useful for motion sickness depresses central nervous system	25 mg b i d or t i d
Plimasin	Pyribenzamine 25 mg and Ritalin 5 mg	1 tab t i d or q i d
Polaramine	The dextrorotatory salt preparation of Chlor Trimeton	2 mg t i d or q i d
Pyribenzamine	Citrate more palatable in liquid than the hydro chloride (in which form it also comes), seda tion moderate gastrointestinal irritation com mon but slight	50 mg t i d or q i d
Pyrrolazote	Similar to Phenergan agranulocytosis has been re ported after excessive dosage	25 50 mg t i d
Tagathen		25 mg t i d or q i d
Theruhistin	Anticholinergic and antiserotonin activity effec tive with minimal sedation unlike the other antihistamines appears to be more effective in bronchial asthma	2 4 mg t i d
Trimeton		25 mg t i d

Sedation —Many patients with severe bronchial asthma are restless and ap prehensive Lack of sleep and inadequate nutrition initiate a vicious cycle in which labored respiration and dehydration combine to accentuate retention of secretions and bronchospasm, and thereby increase obstruction to air flow In other allergic diseases accompanied by severe pruritus, restlessness and insomnia frequently ac centuate the allergic manifestations In the already debilitated patient this cycle of events results in serious deterioration Although there is a manifest hazard in the use of narcotic drugs, some form of mild sedation is *often desirable in the tense* patient who finds it difficult to obtain adequate rest In this connection, obviously, there is no substitute for the ministrations of a calm, confident physician, the re assuring presence of a cheerful nurse, and a relaxing environment

ovide little or no benefit and, in fact, the drying action of these drugs may in-
ease the discomfort These agents are rarely indicated as maintenance therapy
r perennial vasomotor rhinitis They are more effective in acute than chronic
ticaria and occasionally in certain allergic dermatoses, primarily due to their
ntipruritic and local anesthetic effects

Although the response of angioedema is less impressive, the duration and
e of the edematous areas may be reduced While antihistamines are of some
nefit in serum sickness and of questionable value in anaphylactoid reactions,
inephrine, as previously mentioned, remains the drug of choice for these
ates Although in agreement with the general consensus that asthma is not
lped by antihistamines and may in fact be aggravated, Peshkin believes that
ppropriate doses of these drugs are helpful in asthmatic infants who have no evi
nce of respiratory infection Allergic cough in children may also be improved,
it the hazards of such therapy have been discussed in Chapter 28, The Choice
Antitussive Agents The antihistaminic agents have been employed in a num
r of miscellaneous allergic conditions with varying degrees of success Prophy
ctically they have been used in conjunction with blood transfusions and in hypo
nsitization procedures However, present opinion has veered to the view that a
nking reduction in allergic reactions does not take place In certain instances
actions are delayed which may induce a false sense of security on the part of the
nysician. Ophthalmic preparations may provide some relief from the pruritic
mptoms of allergic conjunctivitis but are less effective than the local vasocon
rictors and steroids No beneficial effects have been obtained in the collagen
oup of diseases In common with the other symptomatic pharmacologic measures,
e histamine antagonists suppress certain allergic manifestations but do not affect
e underlying course of the disease

Untoward Effects —All the drugs of the antihistamine group produce un
esirable side reactions, the incidence and severity varying for each of the drugs,
e dosage levels, and the individual response The most common side effect is
xcessive sedation, inability to concentrate dizziness, and disturbed coordination are
lated to this action Frequently this sedative effect begins to wane after 3 or
days, indicating the development of tolerance The combined use of ampheta
ine or an amphetamine like substance such as Ritalin may neutralize some of
e sedative effect In occasional individuals the major untoward effect is that
f agitation or excitation with insomnia, tremors, nervousness, and even convul
ons Other adverse reactions include lassitude muscular weakness, gastroin
stinal disturbances, and urinary retention Dryness of the oropharynx is com
ion of more serious significance is the drying of the mucous membrane of the
ronchi which at times results in intractable coughing, generally unrecognized as
consequence of antihistamines The advantage of local application for the relief
f pruritus may be outweighed by the occurrence of local sensitization to the anti
istamine

A list of some of the more common antihistamines employed in clinical prac
ice is shown in Table 38

Some antihistamines have been incorporated in specialized coatings or matrices
n order to prolong or delay their action The sedative effect of others, such as

upright position Since the dyspnea of intractable bronchial asthma is a constant, chronic burden to the patient, the possibility of *meperidine addiction*, when given subcutaneously, is a real hazard In view of this, it is essential that the program be restricted to a period of 4 to 5 days

Mild side effects include dizziness, loss of appetite, constipation, nausea, and occasional emesis Although no instance of serious respiratory depression has been encountered with the above program in over 300 patients in our clinic, the possible occurrence of such an untoward response must be kept in mind in a hypersensitive individual, especially if barbiturates are also administered In the event that respiratory depression should occur, nalorphine (Nalline) has been demonstrated to antagonize effectively the depressant action of meperidine The depressant effect of meperidine has also been counteracted by caffeine and amphetamine

TRANQUILIZERS —Clinical reports continue to appear in the literature following the recent introduction of the ataractic or tranquilizing drugs It is as yet too early to properly assess the value of these agents in allergic disease since few long term, well-controlled studies have been performed Carryer states that meprobamate and chlorpromazine have been effective in controlling tension in asthmatic patients "with little depression of the respiratory center" We have found meprobamate at times of value in patients with a hyperventilation syndrome, which is sometimes present in cases of pulmonary emphysema as well as bronchial asthma Individual reports have attested to the efficacy of parenteral chlorpromazine in doses of 25 to 50 mg Hydroxyzine (Atarax) and a new phenothiazine compound trimeprazine (Temaril), have been reported as being effective in the treatment of allergic dermatoses and urticaria In addition to being tranquilizers these preparations appear to have some antihistaminic, antiserotonin and anticholinergic like activity By allaying tension and anxiety, these tranquilizing agents aid in reducing the intensity of allergic symptoms in selected patients They have no direct effect on the allergic state and are perhaps best employed as a temporary aid in allergic management While the major side reactions are drowsiness weakness and somnolence there have been a number of reports of a more serious nature including bone marrow depression with agranulocytosis and hepatitis In our opinion the use of reserpine in allergic disease is contraindicated since allergic rhinitis and obstructive dyspnea are often aggravated In addition the superimposition of acute depression has been noted with this drug in tense anxious patients

Modification of Tissue Reactivity With Corticotropin and the Corticosteroids—A decade has passed since Hench and his associates first described the effects of cortisone in patients with rheumatoid arthritis Ample evidence has since accumulated demonstrating that although corticotropin and the adrenocorticosteroids result in remarkable improvement in the clinical manifestations of a wide variety of disease entities, the basic mechanisms involved are as yet unknown Early reports indicated dramatic relief of the symptoms of asthma as well as other allergic diseases such as hay fever, vasomotor rhinitis, and allergic dermatitis in over 80 per cent of the patients treated with these hormones A provocative chapter has been opened by these hormones in the therapy of allergic disease

It has now become evident that (1) they are the most effective agents available today for the symptomatic treatment of a wide variety of allergic conditions

BARBITURATES.—In the past few decades, the barbiturates have become the most widely prescribed agents for insomnia. Small doses (8 to 30 mg.) of these drugs are often incorporated with ephedrine theophylline combinations in order to counteract the excitatory side effects of these bronchodilators. In high dosage or with too frequent administration, particularly in the fatigued dyspneic patient, the barbiturates, like morphine, may depress respiration.

CHORAL HYDRATE.—Because of a low incidence of side effects and rarity of allergic reaction in asthmatic patients, chloral hydrate is the drug of choice for mild sedation. It may be given in doses of 0.5 to 1 Gm. orally or by rectum at 8- to 12-hour intervals without fear of respiratory depression.

ETHER.—In special instances where heavier sedation or bronchodilatation is desired in an effort to terminate intractable bronchospasm, 60 to 90 ml. of ether dissolved in an equal amount of olive oil has been administered rectally as a retention enema. This normally produces restful sleep with good relaxation for a period of 2 to 4 hours. Certain precautions must be observed in the use of rectal ether: (1) constant surveillance during sleep by a nurse and (2) maintenance of a patent airway by positioning the patient on his side with the head of the bed flat.

MORPHINE.—There is universal agreement that morphine is contraindicated in asthma, and there have been several documented instances of death due to obstructive asphyxia or irreversible respiratory acidosis. The deleterious effects of morphine include: (1) central respiratory depression, (2) augmentation of bronchospasm due to cholinergic activity, (3) inhibition of glandular secretion of the bronchial mucosa, (4) diminution of striated muscle tone including the diaphragm and intercostal muscles and (5) suppression of the cough reflex. However, with the use of codeine in the range of 15 to 30 mg. repeated at 4- to 6-hour intervals, we have encountered only minor side effects such as cough suppression and a "drying" action on the bronchial secretions.

MEPERIDINE.—Prior to the introduction of the corticosteroids, meperidine (Demerol) was frequently employed in selected patients with severe intractable bronchial asthma who had become refractory to other forms of bronchodilator therapy. Its use in proper dosage and under close supervision is still warranted to obtain bronchial relaxation in special instances. Pharmacologically, meperidine is anticholinergic and possesses spasmolytic action on bronchial smooth muscle. The development of progressive lack of response to bronchodilator drugs in severe bronchial asthma presents a serious problem when definite contraindications to the use of steroids also exist. One of the simpler methods of restoring sensitiveness to bronchodilator agents in these refractory patients is accomplished by a program of bed rest and the administration of meperidine for a period of 3 to 5 days. This program consists of the intramuscular administration of meperidine 50 mg. every 6 to 8 hours for a period of 4 days. Bronchodilator drugs such as ephedrine, aminophylline, and epinephrine are generally discontinued during this period with the aim of restoring responsiveness to them.

Although less effective, oral meperidine, 50 mg., may at times be substituted for intramuscular administration, but the patient must be cautioned to rest in bed for 2 hours after each dose since vertigo and nausea are more apt to occur in the

CORTICOTROPIN —Except for the special instances when a more rapid effect is desirable, as in status asthma, *longer lasting preparations such as the gel or zinc* salts of ACTH are more commonly employed The usual course in our clinic with the highly purified gel preparation consisted of an *initial dose of 80 mg given* once daily until relief becomes clinically apparent, usually by the second or third day, then gradual reduction in stepwise fashion to 60 mg daily for 2 days, then 40 mg The average duration of a course has ranged between 6 to 12 days Although it is claimed that the zinc preparation produces a smoother and more prolonged ACTH effect, a recent report of the Committee on Drugs of the American Academy of Allergy states that corticotropin zinc and Acthar Gel are of approximately equal therapeutic effectiveness Increased duration of action of the zinc preparation could not be uniformly demonstrated but was considerably easier to administer than the gel For intravenous use, 20 mg of crystalline corticotropin is dissolved in 1,000 ml of 5 per cent dextrose in distilled water with 40 mEq of potassium chloride added This is administered slowly over an 8 to 10 hour period for the first day or two then the longer acting preparations are substituted intramuscularly *Since the intensity of* adrenal cortical stimulation is a direct function of the maintenance of a high level of circulating ACTH, the effects of 20 mg of corticotropin administered in a slow infusion are comparable to 100 to 150 mg of ACTH given by the intramuscular route However for the treatment of allergic disease the corticotropins offer few, if any advantages over the steroids There are two disadvantages, (1) commercially available corticotropin contains foreign protein, and hypersensitive reactions have been reported and (2) it must be given by injection The major usefulness of ACTH is in the prevention of adrenal insufficiency by stimulating endogenous steroid production at the termination of a course of corticosteroid therapy

ADRENOCORTICOSTEROIDS —Because of less interference with electrolyte balance (sodium retention and potassium excretion) and greater activity, *prednisone and prednisolone* have to a large extent, replaced the use of oral cortisone and hydrocortisone *in the treatment of allergic disease* On a milligram for milligram basis the dosage requirement for prednisone is only one third to one fifth that of the older steroids We have been unable to detect any significant differences in either dosage requirement therapeutic effectiveness or toxic manifestations, between prednisone and prednisolone The major principles which govern proper dosage are the administration *of a sufficient amount* of steroid over a long enough period of time to suppress the allergic symptoms, and then establishment of the smallest dose of steroid empirically, which will maintain benefit when supplemented by other symptomatic agents

In severe intractable bronchial asthma *the average course* in the adult patient is initiated by 60 to 80 mg daily in 4 divided doses after meals and on retiring for the first day or two, followed by a decrease of 10 to 20 mg each 2 or 3 days thereafter depending upon the response of the patient *Each dose* of the steroid is routinely administered with milk followed by aluminum hydroxide or calcium carbonate 1 to 2 hours later At the end of 7 to 10 days, an approximate maintenance dose of 5 to 20 mg daily is instituted which frequently requires temporary revision based on the clinical state of the patient Increased *dosage is generally*

(2) the underlying allergic process in all probability is not altered, (3) the pharmacologic activity inevitably results in undesirable side effects, and (4) the more hazardous adverse reactions have given rise to a number of iatrogenic diseases complicating the allergic process While allergic or inflammatory edema appears to be markedly reduced clinically, in vitro studies on sensitized trachea, challenged with histamine or egg albumin showed that contraction was not inhibited by the corticosteroids and is in accord with the observation that these steroids do not prevent experimental anaphylactic shock in animals or interfere with antigen-antibody reactions The physiologic and pharmacologic activity of corticotropin and the adrenocorticosteroids has been extensively studied and the accumulated literature continues to expand rapidly For a better understanding of the clinical role these hormones play in the management of allergic disease and for basic pharmacologic review, the reader is referred to the comprehensive reports by Thorn, Ingle, Kinsell and others

The preparations available at the present time are illustrated in Table 39

Table 39 Corticotropin and Corticosteroids Employed in Allergic Disease

Generic Name	*Type of Preparation*	*Route of Administration*
Corticotropin (ACTH)	Crystalline	Intravenous, intramuscular
	Gel	Intramuscular
	Aqueous zinc	Intramuscular
Cortisone	Tablet	Oral
Dexamethasone	Tablet	Oral
Fludrocortisone	Ointment, lotion	Topical
Fluorometholone	Cream	Topical
Hydrocortisone	Tablet	Oral
	Suspension	Intra articular, intramuscular, aerosol
	Aqueous solution	Intravenous, ophthalmic, nasal spray
	Ointment	Topical
Methylprednisolone	Tablet	Oral
Prednisolone	Tablet	Oral
	Aqueous solution	Intravenous, parenteral ophthalmic nasal spray aerosol
	Ointment	Topical
Prednisone	Tablet	Oral
Triamcinolone	Tablet	Oral

The ingenuity of the organic chemist, stimulated by the more widespread use of these preparations in clinical medicine, will no doubt create newer analogues in which therapeutic efficiency (ratio of activity to side reactions) will be enhanced

Clinical management with these agents must be individualized for each patient since they are nonspecific and the optimum dosage is usually a matter of trial and error based on the clinical acumen of the physician In general, the amounts required are related more to the severity of the disease process than to body weight or age The clinical responses of the patient may be highly variable, requiring frequent changes in schedule to establish the maximal therapeutic benefit with minimal adverse reactions hence patients on steroid therapy should be under close medical supervision It hardly needs to be emphasized that these agents should be employed only after every effort has been made to establish an etiologic diagnosis and to carry out a well conceived program of allergic pharmacologic and physiologic management

although more extensive clinical trials are necessary before the value of this route of administration can be assessed.

Triamcinolone (Aristocort) is a potent corticosteroid with an antiallergic activity slightly greater than that of prednisone. In the maintenance therapy of patients previously on prednisone, approximately 20 per cent less was necessary to maintain remission when triamcinolone was substituted. In contrast to their experience with prednisone, many of these patients reported a decrease in appetite, and a tendency to weight loss. This weight loss may be due in part to appetite suppression, variations in water balance since it enhances sodium and potassium excretion, and increased protein catabolism. In a number of patients on long term maintenance, a peculiar syndrome consisting of headache, weakness, dizziness, and somnolence has been noted. In general this drug produces most of the side effects observed with the other steroids.

Methylprednisolone (Medrol) is also highly effective in the treatment of allergic manifestations. Feinberg and his associates have recently reported that the dose in asthma was comparable to or somewhat smaller than that of prednisone. Like triamcinolone, "methylprednisolone did not show the tendency to cause weight gain as experienced with prednisolone. Part of this was due undoubtedly to the lesser appetite stimulating properties of methylprednisolone." While it has been reported that a more favorable therapeutic ratio of potency to side effects exists with this steroid, adverse reactions in our series have been comparable to those of prednisone.

Dexamethasone (Decadron, Deronil) is a new synthetic corticosteroid with an antiallergic potency reported to be 4 to 6 times as great as prednisone and 25 times that of hydrocortisone on a weight basis. Preliminary studies indicate that at conventional dosage levels this preparation, like prednisone, does not cause excessive salt or water retention or potassium depletion. In our studies it has been appetite stimulating. It is as yet too early to estimate the incidence of side effects peculiar to steroid therapy until additional experience has accumulated on long-term administration.

Fludrocortisone (fluorohydrocortisone) applied to the skin in the form of lotions and ointments has been effective in controlling the manifestations of allergic dermatoses including atopic eczema, contact dermatitis, and neurodermatitis. In this respect it is approximately 10 times as effective as hydrocortisone.

Corticotropin and the corticosteroids are generally not effective for acute "anaphylactic type" reactions which occur within a few minutes in highly sensitive individuals. Here, as already mentioned, epinephrine, subcutaneous or intravenous, is the drug of choice. With delayed reactions accompanied by severe bronchospasm or angioedema, maximal benefit may be obtained with simultaneous administration of intravenous corticosteroid and epinephrine.

[There has not been sufficient experience with fluorometholone (Oxylone) for substantial evaluation. *Ed.*]

Untoward Effects. The hazardous nature of the side effects encountered with these hormones makes close cooperation between the patient and his physician im- [illegible] Since the clinical effectiveness of these hormones requires dosages in ex-

required at times of increased stress such as infection, accidents, surgery, and emotional crises During surgery, for example, it may be necessary to provide an infusion containing 100 mg of hydrocortisone or 50 mg of prednisolone 21 phosphate (Hydeltrasol) which could be repeated 2 or 3 times daily for a period of 2 to 3 days

The duration of a course of steroid therapy must be as highly individualized as the dosage schedule Short intensive courses of prednisone have been found exceedingly useful in tiding the seriously ill patient over an acute episode of bronchospasm or severe serum sickness which is refractory to other forms of therapy In fact, these hormones are the drugs of choice where severe status asthma has been initiated either by an infection or as the result of exposure to increased concentrations of inhalant allergens such as dust or pollens because they will usually control the situation with no necessity for prolonged therapy once the emergency is past

Patients with chronic intractable asthma and the bronchospastic type of pulmonary emphysema unresponsive to conventional forms of treatment must be considered for prolonged maintenance therapy Burrage and his co-workers believe that there is no definite contraindication to steroids and that patients with known duodenal ulcer, osteoporosis or old tuberculosis may have to assume a calculated risk if failure to control asthma is an even greater risk to life Furthermore, maintenance therapy has enabled many of these patients to return to partial or full activity Marked improvement in morale accompanies their "escape" from social and economic invalidism It is desirable that even these patients be regularly "weaned" from the steroids since changes in the allergic state and occasional spontaneous remissions occur during the course of their illness During the tapering off process it may be desirable to administer 60 mg of corticotropin gel daily for one week

There is suggestive clinical evidence that a state of relative adrenal insufficiency may persist for long intervals following withdrawal of hormone therapy This has been illustrated by shocklike states induced by stress such as surgery The reinstitution of steroid therapy before contemplating surgery and maintenance for an adequate period usually ranging between 4 to 7 days has been employed prophylactically in these instances

Topical preparations consisting of aqueous solutions or suspensions of hydrocortisone and prednisolone have been used as ophthalmic drops or nasal sprays for the treatment of allergic conjunctivitis and vasomotor rhinitis These steroid preparations are frequently combined with vasoconstrictors, antibiotics, and antihistamines Such mixtures have become increasingly popular although few data are available concerning the relative effectiveness of the steroid in these combinations A number of recent reports discuss the use of aerosolized steroids in the treatment of bronchial asthma and the insufflation of powder preparations for both seasonal rhinitis and asthma In general, a daily dose of 15 mg of hydrocortisone appeared to be beneficial in hay fever when applied intranasally Approximately 7 5 mg of prednisolone daily in divided doses as an aerosol had the equivalent therapeutic effect of 40 mg of hydrocortisone orally No side effects were reported The usefulness of these steroid aerosols may be in prolonged maintenance therapy

element of bacterial infection is considered to be a primary factor Twelve of the 84 cases reported were demonstrated to have hypogammaglobulinemia prior to treatment From the data thus far accumulated it would appear that the optimum dose is in excess of 0 3 ml per kilogram of body weight administered intramuscularly every 2 to 4 weeks Except for instances in which infection and hypogammaglobulinemia play a role its use at the present time would appear to be unwarranted A longer period of observation is required before any conclusions can be drawn as to the effectiveness of such therapy in asthma uncomplicated by hypogammaglobulinemia

Less Well Defined Therapeutic Objectives—Both nitrogen mustard and artificial fever therapy produced by the intravenous administration of typhoid vaccine or Piromen (polysaccharides derived from *Pseudomonas aeruginosa*) have induced remissions in states of intractable bronchospasm refractory to the conventional bronchodilator agents The mechanism of action has been attributed to a stimulation of endogenous adrenocorticosteroid secretion Prednisone has largely supplanted these procedures in the seriously ill refractory patient Kirk's typhoid vaccine is still occasionally employed in our clinic in selected patients who have shown excellent clinical remissions following a course of fever therapy The usual course consists of 3 intravenous injections of this vaccine administered every other day or at weekly intervals The first dose contains 2 5 to 5 million organisms (0 025 to 0 05 ml), and, depending upon the febrile response this dose is doubled with each succeeding injection Knight prefers subcutaneous or intramuscular Piromen however, we have not been impressed with the efficacy of these routes of administration

The mode of action of Fowler s solution (potassium arsenite) is obscure, but various observers over a period of many years have noted beneficial effects of small doses in patients with intractable bronchospasm A dose of 0 2 ml administered 3 times daily for a period of 7 days is followed by 0 1 ml , 3 times daily for an additional 7 days The hazards of arsenical therapy, particularly by the Gay method have been emphasized by Hansen Pruss and Carryer who caution against the dangers of heavy metal toxicity

Calcium salts are well known agents for the relief of allergic manifestation but their efficacy has never been clearly established Since many of the symptoms of allergy are based on pathophysiologic changes involving capillary permeability a number of investigators have questioned the possibility of a calcium deficiency mediating these changes Epstein and Sevag found that the potassium content of the bronchial secretions in patients with asthma was significantly higher than in patients with chronic pulmonary disease of nonallergic origin They postulated that the potassium loss was due to injury and increased permeability of the cell membrane and that this was corrected by the administration of 3 Gm daily of calcium and potassium glutamate (Capomate) There is no evidence that the salts of calcium affect the mechanisms of allergy and additional well controlled clinical trials are necessary before any conclusions can be drawn as to their clinical benefit

Although they are not pharmacologic agents a complete discussion of the management of allergic disease requires brief mention of psycho and climato

a "Cushingoid" state usually is present The incidence of these reactions appears to bear a direct relationship to the quantity of steroid administered and the duration of therapy Mild side effects such as rounding or "mooning" of the facies, abnormal fat distribution about the pelvis, abdomen, and shoulder girdle, hirsutism, acne, and facial rubor are usual but of only moderate concern Of the more serious side reactions, salt and water retention with potassium depletion encountered with the older steroids has been largely eliminated with the introduction of prednisone

A list of other serious side reactions which have been encountered include (1) alteration in mental state ranging from irritability to frank psychoses, (2) masking or acceleration of infection which accounts at times for the lack of response to steroid therapy, (3) reactivation of pulmonary tuberculosis, (4) gastrointestinal disturbances ranging from dyspepsia and flatulence to serious and even fatal gastrointestinal hemorrhage or perforation of a peptic ulcer, (5) osteoporosis resulting in pathologic fractures, (6) thromboembolic phenomena, (7) aggravation of pre existing hypertension or diabetes and (8), more infrequently, impotence

None of these adverse reactions constitute absolute contraindications to steroid therapy, and ancillary measures are often available to either prevent or lessen the hazards of their occurrence For example, milk, antacids, and occasionally anticholinergic agents aid in ameliorating the gastrointestinal reactions Androgen or estrogen therapy combined with calcium and a high protein intake may serve to mitigate the catabolic and osteoporotic effects of these hormones The administration of 3 Gm of potassium daily is often effective in counteracting excessive potassium depletion The use of appropriate antibiotics and concurrent therapy with antituberculous agents should be promptly instituted when these complications are suspected In this respect adequate screening procedures for detecting such infections, as well as diabetes, must be included in the routine management

In addition, the physician must be aware of the possibility of a 'withdrawal syndrome,' consisting of headache, nausea, vomiting restlessness and muscle or joint pains, following the cessation of long-term therapy Because of the spontaneous diurnal variation in adrenal cortical secretory activity, Di Raimondo and Forsham point out 'When going through the weaning off' process after a high dose suppressive course of corticoids or corticotropin one would do well once down to low dosage, to administer it all in one dose at 8 A M so as to allow the anterior pituitary corticotropin secretion to return gradually while supporting the patient with corticoid when receiving a minimal endogenous supply '

It should be stressed that the aim in long term maintenance therapy should be the relief of severe bronchospasm by the combined employment of bronchodilator drugs, aerosols, and potassium iodide as well as the steroid, and not simply the steroid alone The use of conventional antiallergic measures should be continued in order to decrease the dosage of the steroid hormone to a minimum In this regard the persistence of minor symptoms while on low dosage is preferable to the maintenance of complete suppression of allergic manifestations by high, potentially dangerous levels of hormone

GAMMA GLOBULIN —Modification of tissue, or host, reactivity involving the use of gamma globulin is under study in selected cases of asthma in which the

appointing There is no proof that the effector cell is protected by any of the drugs presently available Future research may delineate the common denominator involved in the allergic reaction With identification of this factor the accomplishment of complete pharmacologic control through specific blocking or barrier action may ultimately take place

Modification of tissue reactivity by the corticosteroids provides symptomatic relief in selected cases of severe self-limited or resistant allergic disease This is accomplished, however, at the price of adverse side reactions which accompany the use of these hormones Of equal importance to the search for newer and safer analogues of the corticosteroids is the employment of these hormones as investigative tools in allergy research

In summary, a list of the more common allergic diseases and the pharmacologic agents employed in their control is presented

Anaphylactoid Reactions Epinephrine—drug of choice Supplementary therapy occasionally with intravenous steroid or intravenous antihistamine Aminophylline intravenously for intense bronchospasm

Serum Sickness Sympathomimetics For severe reactions brief course of steroids or corticotropin

Allergic Rhinitis Se[illegible] ... and environmental control Temporary use of ... tomatic improvement Perer ... identified Oral ephedrine ...

Bronchial Asthma Hyposensitization and environmental control if due to pollinosis Sympathomimetics and theophylline salts—drugs of choice for n ... aeros ... oids ... measures listed Measures to promote bronchial drainage

... Avoidance of food allergen Antihistamines, ephe ... topical vasoconstrict ...

Atopic Dermatitis Environmental control including discontinuance of responsible drug, food, or contactant Oral ephedrine Dermatologic preparations including topical steroids if severe Brief course of antihistamines if pruritus is severe

Urticaria Similar to allergic dermatitis, antihistamines are effective in the acute form ... Concurrent use with intra ... nx ... ffective in controlling symptoms Antiasthmatic regimen in prese... bronchospasm

A half century has passed since allergy was first recognized as a distinct clinical entity During this time basic knowledge concerning the mechanisms of the allergic process have been applied only sporadically to therapy Most of the drugs employed in the treatment of allergic disease today leave much to be desired In seeking a rational basis for newer agents the ideal characteristics to be considered are (1) a universal preparation affecting all allergic manifestations by neutralizing ... een the shock tissue and the humoral agents which

therapy Much has been written about the psychodynamics of the allergic personality, and it is apparent to the practicing physician that the acute allergic attack is often accompanied by emotional disturbances Support for the emotional factors in triggering and maintaining allergic symptoms is partially supported by evidence presented by Tuft, who showed that 80 per cent of children with severe asthma had marked relief when separated from their home environment This study was controlled to exclude the effects of changes in climate or removal from specific allergen exposure In our experience hyperventilation of nervous origin results at times in serious aggravation of asthma with increased trapping of air and broncholaryngospasm

The benefits of temporary residence in a pollen free area for the treatment of hay fever and pollen asthma have already been discussed Aside from this short term environmental control, the advantages of climatotherapy involving permanent relocation continue to appear in the literature It is the opinion of most authorities, and of the authors, that such therapy involving numerous hardships with socioeconomic derangements and the frequent breaking up of the family unit, is not warranted in view of the equivocal benefit derived In this connection, Gottlieb suggests that this form of therapy more often than not, may be a measure of desperation

DISCUSSION AND SUMMARY

The very nature of the allergic process involving as it does almost every cell and tissue of the body, makes any discussion of pharmacologic therapy necessarily cumbersome and involved Specific therapy limited at the present time to hyposensitization and environmental control has many serious drawbacks Even in those instances where the offending allergen has been positively identified, these forms of therapy may be impractical For example, certain manifestations of allergic disease occur rapidly and are fulminating, requiring immediate correction not possible with the specific measures mentioned above In other instances eco

in the environment or treatment with injections of suitably selected allergenic extracts"

Unfortunately, it has not been possible to identify the specific allergen in a majority of patients suffering from allergic disease In many of these individuals, multiple factors are operative in the causation of symptoms For this entire group as well as those afforded incomplete relief with hyposensitization, symptomatic therapy constitutes the only avenue of control Antihistaminics and corticosteroids, while contributing much to the pharmacologic treatment of allergic states, are simply additions to symptomatic therapy and have not provided any solution to a quest for a universal, specific antiallergic drug In this regard, the idea of 'barrier therapy" possesses considerable merit However, most of the drugs which serve as a barrier between the cells and those substances such as histamine, acetylcholine, and serotonin, believed to mediate the allergic response, have been dis-

Aerosol Therapy, Dis
f Ragweed Pollen From
56
od, New York J Med
57 1429, 1957
Segal, M S, Dulfano, M J, and Herschfus, J A Advances in the Physiology and Treat
Sherman,
Sherwood
Thorn, G
Tuft, L., 203 717, 1942.

are responsible for the allergic response, (2) decreased incidence of toxicity, which at the present time seriously limits the more effective agents in use today, and (3) sustained, effective action with absence of tolerance. Intensification of research in this field initiated within the past 5 years holds much promise for the future.

SELECTED REFERENCES

Arbesman, C A Newer Drugs for Relief of Allergic Diseases, New York J Med 56 3678, 1956

Barach, A L Rectal Instillation of Aminophylline in Intractable Asthma, J A M A 128 589, 1945

Barach, A L Remissions in Bronchial Asthma and Hypertrophic Pulmonary Emphysema, J A M A 147 730, 1951

Barach, A L, and Bickerman, H A Pulmonary Emphysema, Baltimore, 1956, The Williams & Wilkins Co

Barach, A L, Bickerman, H A, and Beck, G J Clinical and Physiological Studies on the Use of Metacortandracin in Respiratory Disease I Bronchial Asthma, Dis Chest 28 515, 1955

Bickerman, H A, Beck, G J, Itkin, S, and Drimmer, F Evaluation of Oral Bronchodilator Agents in Patients With Bronchial Asthma and Pulmonary Emphysema, Ann Allergy 11 301, 1953

Black, R L, Yielding, L K, and Bunim, J J Observation on New Synthetic Antirheumatic Steroids and Critical Evaluation of Prednisone Therapy in Rheumatoid Arthritis, J Chron Dis 5 751, 1957

Blumenthal, J S, Brown, E B, and Campbell, G S Molar Sodium Lactate in Acute [illegible] Patients, Ann Allergy 14 506 1956

1956

Burrage, W S, Greene, J E, Burgin, L B, Itkin, I H, Novey, H S, Engler, J, and Irwin, J W Medical Progress Allergy, New England J Med 255 79, 128, 1956

Carryer, [illegible] 82, 1957

Cooke, R [illegible] Co

Cooke, R [illegible] 6

Digilio, [illegible] Therapy

Di Raim[illegible] of the [illegible] J Med 21: 321, 1956

Dragstedt [illegible]

Farber, S [illegible]

Feinberg, [illegible]

[illegible]

1 330, 1946

Irwin, J, [illegible] al Asthma'

Kabat, E [illegible] Reactions [illegible] Medicine,

Kinsell, I [illegible] nal Steroid

Knight, [illegible] ders, Ann Allergy 12: 174, 1954

Hypercholesterolemia—Treatment of hypercholesterolemia with estrogen is still in the experimental stage Large doses have been used 0 25 to 1 mg of ethinyl estradiol a day corresponding to 2 500 to 10 000 rat units With women it is quite possible to give estrogens over a long period provided progesterone is given 4 days out of each month Men will become feminized with this dosage of estrogen, and for that reason the treatment is seldom acceptable to them

The evidence thus far available does not justify recommending estrogen as a regular preventive of atherosclerosis even in women, but it may be tried in familial hypercholesterolemia. There has been no adverse effect on women who have been treated as long as a year and a half in the small group thus far studied

Several studies have now been reported indicating that nicotinic acid is effective in lowering elevated blood cholesterol to normal levels Three to 6 Gm a day is required by mouth There is almost invariably an uncomfortable flush after each dose the first 3 days, but this usually disappears by the end of a week Pruritus occasionally occurred too during the first few days of treatment No serious toxic effects have thus far been encountered Further study will have to be done to determine whether the lowering of the blood cholesterol level reduces atheroma formation or reverses atherosclerosis

Hyperlipemia—Increase of neutral fat in the blood or hyperlipemia, is a different kind of disorder of blood fat and is affected by agents other than those that tend to reduce the blood cholesterol level Some untreated diabetics develop gross hyperlipemia so that the blood may contain 6 to 8 Gm or more of neutral fat per 100 ml Small doses of insulin may clear the blood of this excess fat within a few hours

HEPARIN—After eating a fatty meal everyone tends to have a transient physiologic hyperlipemia, the disappearance of which cannot be speeded up with insulin Heparin acts rapidly to clear the blood of neutral fat within a few minutes after an injection of heparin the plasma is perfectly clear The mechanism of this action has been studied extensively but is not yet thoroughly understood

Familial Hyperlipemia—There is also a condition known as familial hyperlipemia in which patients have a hereditary defect in the ability to eliminate fat from the blood At each meal the fat ingested accumulates until very large quantities of neutral fat are present and the plasma has the appearance of cream Neither insulin nor heparin will assist in clearing the blood of fat in this instance, but spacing of fat ingestion over several days will control the condition

Diet and Atherosclerosis—Aside from its effect on the blood cholesterol a diet low in calories seems to protect people from serious atherosclerosis as evidenced by coronary artery disease Such diets usually have a relatively small proportion of fat and this has focused attention on the question of whether the type of fat makes a difference Evidence is now beginning to appear relating the type of fat in the diet to atherosclerosis The highly saturated fats like butter fat and lard appear to be more deleterious in this regard than the unsaturated fats like corn oil peanut oil, and fish oils A carefully controlled study of Ahrens suggests that corn oil in the diet in place of butter fat will actually cause blood cholesterol to be decreased by raising its rate of excretion There are no specific therapeutic implh

except that people in middle life may be well ad

THE CHOICE OF DRUGS IN CERTAIN DISORDERS OF METABOLISM

George G. Reader, M D.

INTRODUCTION

A group of pharmacologically active agents that owe their use to their ability to alter body metabolism in some highly selective way may well be considered together These include the lipotropic agents which are of use in lowering blood lipids, antipyretic drugs, drugs which alter the metabolism of alcohol to make it intolerable to the body, and insulin and other drugs that alter carbohydrate metabolism

LIPOTROPIC AGENTS AND ATHEROSCLEROSIS

Elevation of levels of blood lipids and particularly of cholesterol, which occurs in a variety of conditions such as myxedema, untreated diabetes, nephrosis, and familial hypercholesterolemia and in many otherwise normal American men and woman is thought to increase the tendency toward formation of atheromas, thus leading to severe atherosclerosis, arterial thrombosis, and occlusion The effect is most evident in patients with extremely high levels of serum cholesterol, above 400 mg per 100 ml, a high proportion of whom develop severe atherosclerosis

Thyroid Hormone —Various agents may be effective in altering blood cholesterol Thyroid is known to lower the blood cholesterol, and the use of preparations containing thyroxine will regularly diminish the concentration of cholesterol in the blood This is most evident in myxedema but is seen in normal people as well if enough thyroid hormone is given

Estrogens and Androgens —Other hormones that affect blood cholesterol are estrogens and androgens, the former tending to reduce the levels, and the latter to raise them Not only is the absolute level of serum cholesterol modified, but the cholesterol phospholipid ratio is altered as well, toward normal with estrogen and away from normal with androgen In myxedema, for instance, estrogen will reduce the cholesterol level even when thyroid is omitted and when the basal metabolic rate still remains low Treatment by estrogen in patients with familial hypercholesterolemia and xanthomatosis affects lipid relationships favorably and, in some, results in return to normal concentration and distribution of cholesterol and phospholipids

effective Disulfiram is absorbed *fairly rapidly* from the alimentary tract but is much more soluble in fat than in aqueous solutions It may be that the fat depots take up most of the drug for some period before sufficient amounts can accumulate in the circulation to produce the characteristic effect

Once the patient has taken his morning dose of either disulfiram or CCC he knows that he cannot drink *for at least 3 or 4 days* This provides him with a breathing spell wherein effective psychotherapy may be started If he does ingest *alcohol the patient will* soon note flushing of the face followed by nausea and vomiting and in severe reactions by hypotension to shock levels *Calcium carbimide* is considered to be preferable for long term treatment because it has fewer disagreeable side effects of its own Disulfiram may tend to cause *acneiform* eruptions lassitude fatigue sexual impotence, headache, and dizziness all of which are said not to develop after calcium carbimide

INSULIN, ORAL ANTIDIABETIC DRUGS, AND DIABETES

Diabetes mellitus is a disease characterized by a defect in *carbohydrate metabolism so that blood glucose* is not utilized by the tissues There is a drop in blood *sugar* levels with the administration of insulin and for treatment of the diabetic patient a variety of insulins have been prepared

Regular Insulin —*Regular insulin is an aqueous solution of the active hormone* of the pancreas which affects the metabolism of glucose Presumably the glucose concentration of the blood ordinarily determines *how much hormone the pancreas* puts out into the circulation In the diabetic patient, however, when the insulin must be administered parenterally, regular insulin has a prompt effect on the blood sugar but is rapidly metabolized so that frequent doses must be given in order to keep the blood sugar at normal levels Regular insulin still finds considerable use in treatment of diabetic acidosis and for the patient who is suffering an intercurrent infection or having an operation but for ordinary use some means of delaying absorption by *modification of the* insulin is usually employed

Long Acting Insulins —

Protamine Zinc Insulin —Protamine zinc insulin (PZI) *is insulin which is* combined with zinc and with protamine derived from the sperm of fish It forms a complex with an isoelectric point at pH 7 2 and is *only slowly* absorbed *from* body fluids so that an amount injected will often be active in depressing blood sugar for 48 to 72 hours

Globin Zinc Insulin —Globin zinc insulin is a complex of insulin with zinc and the globin from beef hemoglobin which has a shorter duration of action than *protamine zinc insulin but longer than regular*—16 to 24 hours

Isophane Insulin —Isophane insulin is also known as NPH insulin It is a controlled preparation of protamine zinc insulin which has a *duration of action* of 28 to 30 hours

Lente Insulins —The newest insulin preparations are the lente insulins developed by Hallas Moeller They are regular insulins modified by combination with zinc A suspension of amorphous insulin and zinc particles, called semilente

vised to avoid a large amount of fat in their diets particularly dairy products, and should attempt to substitute corn or peanut oil for animal fats when possible

[A large scale long term study of the effect of the so-called low cholesterol diet on already existing atherosclerosis is now under way Ed.]

Ineffective Agents—Choline and methionine have been known to restore liver tissue to normal when it has been infiltrated with fat but there is no evidence that either of these two drugs affects blood lipid levels or atherosclerosis Similarly sitosterol which is the plant analogue of animal cholesterol has had no demonstrated effect on patients with abnormal blood lipids when administered over a long period of time nor has it shown any tendency to lessen atherosclerosis These agents alone together or mixed with vitamins are of no value and should not be recommended for treatment or prevention of atherosclerosis

ANTIPYRETIC AGENTS AND FEVER

Fever is a physiologic response to a foreign protein and probably represents a manifestation of an important defense mechanism Unless it becomes so high as to raise the question of damage to protoplasm it is probably best ignored and may even be considered beneficial At dangerous elevations physical means of reducing body temperature are more satisfactory than pharmaceutical methods but occasionally a patient can be made to feel more comfortable by administration of antipyretics

The two that are most satisfactory are the salicylates and acetophenetidin Both act on the heat regulating mechanism of the central nervous system to cause a greater dissipation of body heat through cutaneous vasodilatation

The antipyretic dose of salicylates and of acetophenetidin is from 0 3 to 1 Gm orally every 3 to 4 hours

ANTIALCOHOLIC DRUGS AND ALCOHOLISM

Alcoholism is a complicated disease of personality maladaptation whereby the patient seeks to nullify the painful aspects of his environment through ingestion of large amounts of alcohol One approach to treatment is to administer a drug to the patient that causes alcohol to produce marked toxic symptoms This serves to prevent the ingestion of alcohol and conditions the patient against it If the personality disorder is not too firmly fixed and alternative forms of adjustment exist for the patient he may be induced to give up alcohol and will continue to get along without it after weaning Usually the antialcoholic drugs are at best adjuvants to psychotherapy for the alcoholic patient

Disulfiram and Citrated Calcium Carbimide—Two drugs are available disulfiram (Antabuse) and citrated calcium carbimide (Temposil CCC) Both act in much the same way to inactivate one or more enzymes which are required to oxidize acetaldehyde The sensitizing drugs not only cause an accumulation of acetaldehyde after alcohol ingestion but may also alter the vascular reaction to acetaldehyde

With citrated calcium carbimide all subjects have been sensitized with a single dose of 50 to 100 mg whereas with disulfiram a single dose may or may not be

Chlorpropamide (Diabinese) is more potent than tolbutamide, partly because it is more slowly excreted It may be given in doses of 500 mg or less daily Geriatric patients may be more sensitive to the hypoglycemic effects and should be started on no more than 250 mg daily As much as 1 Gm may be required by younger patients, but doses higher than this should be avoided Serious drug reactions have been reported with toxic effects on the liver in a few cases, and the drug should be used with caution

The hypoglycemic effect of the biguanides such as phenformin (DBI) results from decreased glucose output by the liver and increased glucose uptake by the muscles Insufficient clinical studies have been carried out with this group of drugs to know what place they may have in the future management of diabetes They frequently cause nausea and vomiting, which will probably limit their usefulness

SELECTED REFERENCES

Achor, R W P, Berge, K G, Barker, N W, and McKenzie B F Treatment of Hypercholesteremia With Nicotinic Acid, Circulation 17 497, 1958

Ahrens E H, Jr, Blankenhorn, D H, and Tsaltas T T Effect on Human Serum Lipids of Substituting Plant for Animal Fat in Diet, Proc Soc Exper Biol & Med 86 872, 1954

Barr, D P Some Chemical Factors in the Pathogenesis of Atherosclerosis, Circulation 8 641, 1953

Beaser S B Diabetes Mellitus New England J Med 259 525, 1958

Done A K [illegible] cs 23 774, 1959

Ferguson [illegible] G A New Drug for Alco[illegible]

Gilder, [illegible] Effect of Hormones on the [illegible] 957

Goldner, [illegible], A M A Arch Int Med 102 830 1958

Haunz, E A Clinical Evaluation of Lente Insulin in 109 Diabetic Patients J A M A 159 1611 1955

Jost, F Blood Dyscrasias Associated With Tolbutamide Therapy, J A M A 169 1468, 1959

Krall L P, and Bradley, R F Clinical Evaluation of Formamidinyliminourea a New Biguanide Oral Blood Sugar Lowering Compound Comparison With Other Hypoglycemic Agents, Ann Int Med 50 586 1959

Martensen Larsen O Five Years Experience With Disulfiram in the Treatment of Alcoholics Quart J Stud Alcohol 14 406 1953

Keyes, A The Diet and the Development of Coronary Heart Disease, J Chron Dis 4 364, 1956

Keys A and Buzina R Blood Coagulability Effects of Meals and Differences Between Populations Circulation 14 479 1956

Stadie, W C Current Views on the Mechanisms of Insulin Action, Am J Med 19 257, 1955

Symposium Insulin and the Oral Hypoglycemic Agents Part II, Metabolism 8 469, 1959

Unger, R H and Davidson J W Current Status of Aryl Sulfonylureas in Treatment of Diabetes Mellitus, J A M A 162 447, 1956

of large particle size is called ultralente and has a duration of action of over 30 hours A third preparation is a suspension of insulin crystals of small particle size (lente) which has a duration of action of approximately 24 hours

The lente insulin now on the market is a mixture of minute particles of crystal line zinc insulin and amorphous zinc insulin in proportions of about 70 and 30 per cent, and is relatively insoluble at the pH of the blood Because no foreign protein other than insulin itself is included, the danger of allergic reactions is less Lente insulin can be substituted for isophane insulin on a unit for unit basis, but usually slightly less is required for satisfactory control

Choice of an Insulin Preparation—In the treatment of the diabetic patient insulin is preferable to any of the oral hypoglycemic agents in the patient who develops his diabetes in childhood or early adult life The type of insulin to be used depends upon the clinical situation Regular insulin is best when the patient is first being regulated, in the presence of infection or acidosis, or immediately before and after surgery It may be given intravenously when absorption might be delayed from a subcutaneous site in severe acidosis or shock

One of the longer acting insulins should eventually be chosen for those diabetic patients who require insulin at all because of the ease of management with one injection per day Lente insulin would appear to be satisfactory as far as uniformity of response over 24 hours from one dose is concerned but its advantages over NPH are slight Actually NPH and globin insulins are entirely adequate, and it is possible to learn to use any one of the long acting insulins with complete satisfaction Some physicians prefer to tailor the dose of long acting insulin to their patient's needs by mixing PZI and regular insulin to get the exact amount of prolongation of action required The excess of zinc in the PZI acts to prolong the action of the regular insulin mixed with it

Oral Antidiabetic Drugs—There are presently three agents available that may be given by mouth to produce a hypoglycemic effect These are the sulfonylureas (tolbutamide [Orinase] and chlorpropamide [Diabinese]) and the biguanide (phenformin [DBI]) Analogues of DBI the amyl and isoamyl biguanides are not available on the commercial drug market at this time

The sulfonylureas supposedly cause increased insulin activity, possibly by a direct stimulation of insulin production in the islet cells Their best use is in older diabetic patients in whom it has been shown that tolbutamide, according to most authorities, is a safe substitute for insulin They are dangerous in brittle diabetic patients and in young diabetic patients because ketosis may occur despite adequate dosage Some physicians have claimed better control of brittle diabetes with a combination of sulfonylurea and insulin but this work must be further evaluated

The recommended dosage of tolbutamide (Orinase) is 1 Gm daily A few patients respond only to higher dosage sometimes as much as 3 Gm a day Patients should continue to test their urine carefully for glucose and ketones and the dosage should be altered accordingly or insulin therapy substituted [Blood dyscrasias have been noted With the increasing use of tolbutamide, the literature should be followed for further reports on toxicity of this drug as well as of the other oral hypoglycemic agents Ed]

THE PITUITARY GLAND

The pituitary gland, the governing agent of the endocrine system, is concerned with the secretion of a large number of hormones The pituitary hormones are protein in nature and may be classified into two categories based upon their specific effect—a direct one upon metabolic processes of the body (growth hormone or vasopressin) and an indirect one which induces its effects through an intermediary organ e g, the gonadotropic hormone, which in the absence of the gonads is without demonstrable activity

The pituitary gland is divided into two principal portions, the anterior lobe and the posterior lobe Between the two lobes is the intermediate lobe, the function of which is problematical inasmuch as no specific hormones, with the possible exception of the melanophoric hormone, have been established as being secreted by the intermediate lobe The anterior lobe produces a number of different specific hormones which have been more or less characterized as separate entities in recent years

The four types of cells in the pituitary gland are chromophobes acidophils, basophils and amphophils The chromophobes presumably have no endocrine secretion and as stem cells give rise to the chromophils The specific hormones which have been extracted from the anterior lobe are the adrenocorticotropic hormone (ACTH) the thyrotropic hormone (TSH), the gametogenic hormone, which is also referred to as the follicle stimulating hormone (FSH), the luteinizing hormone or interstitial cell stimulating hormone (ICSH), the luteotropic or lactogenic hormone and the growth hormone, also referred to as the somatotropic hormone

The posterior lobe of the pituitary gland is responsible for two hormones only—the vasopressor substances and oxytocic hormone The vasopressor hormone also possesses antidiuretic hormonal activity There is some disagreement whether the posterior lobe actually produces these hormones or whether they are secreted into the posterior lobe from more or less specific hypothalamic areas The precise chemical structure of the posterior lobe hormones have been identified and synthesized This has yet to be accomplished for the hormones secreted by the anterior lobe

Anterior Pituitary Hormones

Growth Hormone —The growth or somatotropic hormone presumably arises from the acidophilic cells The therapeutic use of growth hormone in the past has not been very effective in inducing adequate growth in stunted or dwarfed children The growth hormone preparations on the market at present cannot be considered as being therapeutically active and are of little value More recently, with the availability of human growth hormone and that produced from the glands of the Rhesus monkey, there is evidence to indicate that such preparations may well be effective clinically Preliminary data indicate that growth may be induced in children who are undersized Unfortunately, this material is available for only limited use Recent evidence has indicated that partial digestion with proteolytic enzymes of the growth hormone extracts prepared from the glands of animals may so alter the preparation that physiologic effects may be noted in human beings

THE CHOICE OF DRUGS IN ENDOCRINE DYSFUNCTION

Herbert S. Kupperman, M.D.

INTRODUCTION

With the advent of thyroxin and adrenaline, the first hormones of the endocrine system to be crystallized, endocrinology raised its head during its infancy Further developments led to the ultimate condemnation of the prevalent empirical therapy with the crude glandular extracts then available Particularly in the last two decades, there has been a flood of newer crystalline hormonal preparations which have been available to the physician for the treatment of different endocrinopathies and allied conditions In addition, their use, not only for therapy but for diagnostic purposes, has led to greater diagnostic acumen and eventual therapeutic application

The hormone preparations which are available to date may be divided into the steroidal and the nonsteroidal substances The steroidal hormones are classified on the basis of their chemical structure The lipid-soluble substances or steroidal hormones are produced by the glands of internal secretion derived from the mesoderm The nonsteroidal hormones are secreted by those endocrine glands which have their origin in the ectoderm

Hormones have been used for several different specific purposes They, of course, are available to supplement or replace the function of any specific gland They are also used for pharmacologic effects which have no relationship at all to any endocrine deficiency disease (e g, corticoids in pemphigus and rheumatoid arthritis) Hormones are used to inhibit the function of certain endocrine glands (e g, thyroid hormone to inhibit the thyroid-stimulating, or thyrotropic, hormone (TSH) of the pituitary gland and thereby to help in the treatment of exophthalmos) They are also employed to induce a more nearly normal physiologic state in certain instances where there may be no precisely determined deficiency, but where the endocrine preparation is used for its specific pharmacologic activity and not as a replacement substance (e g, corticoids in refractory edema and insulin in anorexia) In this chapter the disease entities and hormones of each specific endocrine organ will be considered separately

administration of parenteral ACTH in such persons does not represent a propitious form of therapy

The use of ACTH is paramount in delineating between primary or secondary adrenal insufficiency The administration of 40 units of ACTH gel should result in an appreciable increase in 17-hydroxysteroids in the blood within 3 to 4 hours after the intramuscularly administered injection In the event that there is no increase in 17 hydroxysteroids in the blood one can assume that the patient has adrenal glands incapable of functioning either because of complete suppression by exogenous corticoids or because of destruction by some pathologic process The management of patients with either primary or secondary adrenocortical insufficiency however would still be the same and would entail the use of oral corticoids Hence, the ACTH procedure is important, purely from the aca demic point of view, in differentiating between primary and secondary hypo-adrenocorticoidism

Diagnostically ACTH has been employed to determine the presence or ab sence of hypofunction or hyperfunction of the adrenal gland, as well as to differen tiate *between hyperplasia and neoplasia in certain hyperadrenal corticoid states* The use of ACTH in determining the extent of increased adrenocortical ac-tivity is particularly applicable to patients with Cushing's syndrome, for in these persons enhanced responsiveness of the adrenal cortex may be observed While the absolute value of excretion of the steroids from the adrenal cortex may be rela tively small, the marked increase in activity induced after ACTH is administered is of the utmost importance in determining the presence or absence of Cushing's syndrome Once a diagnosis is made the treatment of this disease is surgery Hence it is imperative that the provocative test with ACTH assume an important place in the diagnostic armamentarium of the physician called upon to differenti ate between Cushing's syndrome and allied clinical entities

The procedure entails the administration of *either 40 units of ACTH gel intra* muscularly or 25 units of ACTH intravenously as an aqueous solution The *17-hydroxysteroids in the blood* are determined before ACTH administration and 3 to 4 hours after the intramuscular injection, or immediately after an 8 hour infusion with the ACTH solution Urinary 17 hydroxysteroids and 17 ketosteroids are determined for 24 hours before the ACTH administration as well as for 24 hours after the intramuscular injection of ACTH, or at 8 hour intervals if ACTH is given intravenously The 8 hour periods of urine collection are set up as fol-lows *The 8 hours before ACTH* infusion, *the 8 hours during the infusion,* and the 8 hours after the infusion has been completed

In a patient with Cushing's syndrome the blood 17-hydroxysteroid level will exceed 50 gammas per 100 ml and *the urinary* 17 hydroxysteroid excretion will exceed 50 to 60 mg per 24 hours after the injection of ACTH Patients receiv-*ing the infusion* will have a comparable rise in urine and blood levels

In patients in whom an elevated urinary 17 hydroxysteroid level is already present and in whom the blood 17 hydroxysteroids are also markedly elevated but in whom no changes occur after ACTH injection, the possible diagnosis of adrenal neoplasm must be considered However, one must be cognizant of the fact that more and more patients with adrenal neoplasm are being *recognized who still show*

There are certain undesirable side effects that growth hormone may induce which would ordinarily limit the widespread use of this preparation, the principal one being the creation of a diabetic like state in some patients receiving therapeutically effective doses Obviously, in a potentially diabetic patient this may be disastrous In addition the animal preparations have the ever present possibility of inducing antihormone production

Thyrotropic Hormone (TSH) —In recent years the thyrotropic hormone has been made available for diagnostic purposes It plays no part in therapy inasmuch as the treatment of thyroid insufficiency secondary to pituitary hypofunction is readily managed by the administration of any one of the many oral thyroid preparations available However, TSH has an important place in the physician's diagnostic armamentarium in differentiating between primary and secondary hypo thyroidism The patient with primary hypothyroidism will show no response to a test dose of 5 I U of TSH administered each day for 3 days On the other hand hypothyroidism secondary to pituitary failure would result in a more nearly normal thyroid state under the influence of the TSH administered as previously stated Diagnostically it is conceivable that TSH administration may differentiate anaplastic thyroid disease from nonanaplastic thyroid disease Theoretically a carcinoma of the thyroid gland will not respond to TSH Hence, this preparation may be useful in differentiating anaplasia from hyperplasia in patients with thyroid nodules

Adrenocorticotropic Hormone (ACTH) —Adrenocorticotropic hormone found a useful place in therapeutics with the demonstration of the action of corticoids upon certain collagen diseases The diagnostic use of ACTH is also of impor tance While its principal effect is achieved by stimulating the adrenal cortex to greater secretion, ACTH may also have a primary effect upon raising blood lipid and cholesterol levels in the absence of the adrenal gland

Therapeutically ACTH may be used to supplement or replace the corticoids in the different collagen diseases It may also be used therapeutically to enhance the activity of the patient's adrenal gland The importance of ACTH in clinical medicine is due in part to its enhancing adrenocortical activity in patients in whom suppression of endogenous ACTH secretion has occurred as a result of corticoid therapy The use of ACTH in these persons may at times be important in maintaining the function of the adrenal cortex which otherwise would have been completely suppressed indeed to the point of adrenal atrophy as a result of exogenous corticoids The combined use of ACTH and corticoids is a rational form of therapy in those diseases in which endogenous corticoid elaboration may be more helpful than the use of cortisone alone It has been suggested that ACTH is more effective in the management of certain hematologic diseases as well as in conditions of stress Therapeutically ACTH may be employed in the treatment of severe allergic manifestations associated with dermatitis venenata, in which en hancing the function of the adrenal gland of the patient may at times result in a better therapeutic response than that obtained by the use of cortisone alone ACTH therapy has no place in the treatment of patients with secondary adrenal insufficiency due to pituitary insufficiency Inasmuch as oral therapy with corticoids will more than amply supplement the needs of the patient, the chronic

age Failure for this development to occur by the age of 14 or 15 years must be considered evidence of delayed puberty Consequently, the physician's clinical judgment must be tempered by the patient's appearance and the age of the patient in determining whether therapy is indicated

In addition, the 17-ketosteroid assay is a valuable laboratory test in determining the existence of hypogonadism Normally in boys up to the ages of 8 or 9 the maximum 17 ketosteroid excretion is 1 mg per 24 hours per year of life Values which are considerably below this must be considered as evidence of depression and, if present, together with the clinical manifestations of hypogonadism would indicate the need for active therapy

Another important criterion listed above is the psychosomatic need of the patient There is nothing so cruel as the ridicule of the friends who may be aware of a young patient's affliction In order to prevent damage to the psyche of these hypogonadal boys and to prevent feelings of inferiority associated with abnormal behavior patterns of overcompensation, it is of the utmost importance that therapy be instituted The beneficial effects are not only observed in a change in the overt behavior of the boys, but also by normal external genital development when the child matures sexually

The doses of chorionic gonadotropin employed for the treatment of hypogonadism have been arbitrarily set 1,000 I U, 3 times a week for 3 weeks, followed by 1,000 I U twice a week for 3 weeks in children above the age of 10 years Children under 10 received one half this dose in the same manner

CRYPTORCHIDISM —Cryptorchidism, or failure of the testes to descend bilaterally or unilaterally, may or may not be associated with hypogonadism Therapy for undescended testicles is not predicated upon the presence of hypogonadism but upon the need to bring the testes down from the abdomen into the scrotum Irreparable damage to spermatogenesis may take place if the testes reside in the abdomen Hence, treatment of cryptorchidism should be initiated as soon as a diagnosis is made, after the age of 5 years Therapy consists of the administration of chorionic gonadotropin in doses comparable to those listed above for hypogonadism If descent of the testes fails to occur, the patient must then be considered a candidate for orchiopexy, inasmuch as irreparable damage, resulting in sterility in the bilateral cases, may occur if the testis is left in the abdomen The sooner the testis is brought down into the scrotum the less likely the possibility of damage

OLIGOSPERMIA —The use of chorionic gonadotropin at the present time for the treatment of adult males with oligospermia is of little value and must be considered experimental This is based upon the present knowledge of the factors controlling spermatogenesis While there is a need for androgenic substances to maintain spermatogenesis the primary effect of human chorionic gonadotropin is to stimulate androgenic production by interstitial cell hyperplasia Spermatogenesis requires follicle stimulating hormone activity Very little or none is present in human chorionic gonadotropins

HCG IN THE FEMALE —The use of chorionic gonadotropin in the female has little or no therapeutic value As a matter of fact, its use in the female in whom

an increased response to ACTH This may at first appear paradoxical It is difficult to explain in the light of our present knowledge in that an adrenal neoplasm is thought to be independent of pituitary control Since it is now clear that ACTH may stimulate adrenal neoplasms the concept that an adrenal neoplasm lives unto itself needs revision

Gonadotropic Hormone —Although there are several types available for use clinically the gonadotropic substances which are used most widely in medicine are those prepared from the urine of the pregnant human female and those obtained from the serum of the pregnant mare The other pituitary gonadotropins have not been used much in recent years because they may induce antihormone production

Human chorionic gonadotropin (A P L) is primarily luteotropic and luteinizing in effect in the female and interstitial cell stimulating in the male In other words this hormone is important in maintaining the function of the corpora lutea in the female thereby enhancing the secretion and production of progesterone, and in enhancing testosterone and estrogen production from the Leydig cells in the male However the clinical use of chorionic gonadotropin should be primarily confined to the male There is little or no evidence that this hormone is therapeutically important or significant in the female

Therapy with human chorionic gonadotropin (HCG) in the male may at times be accompanied by the development of gynecomastia It is wise, therefore before HCG is administered to discuss this possibility with prospective patients or parents so that the appearance of mastodynia or mazoplasia is not regarded as an unexpected catastrophe The Leydig cells apparently having a biphasic potential will secrete estrogens as well as testosterone or the increased amount of testosterone may be degraded partly into estrogen Whatever the mechanism may be sufficient estrogen like substances may be formed to induce significant gynecomastia The gynecomastia developing during chorionic gonadotropin therapy is seen primarily in the prepubertal or pubertal boy and is akin to the spontaneous gynecomastia noted during puberty occurring as a result of endogenous testicular stimulation Gynecomastia seen with HCG therapy is an undesirable albeit physiologic, expression of testicular stimulation It will as in most cases of pubertal gynecomastia subside without residual effects There is no specific hormonal therapy at the present time capable of preventing exogenously induced gynecomastia or of nullifying endogenous gynecomastia

Male Hypogonadism —The use of chorionic gonadotropin in the male is confined to hypogonadism for both therapeutic and diagnostic purposes In addition it may also be used as a therapeutic test in patients with cryptorchidism in an attempt to induce descent of the testes The he
tropin in the hypogonadal male is warrar
fulfilled (1) clinical evidence of hypogo
velopment of the phallus and the testes or the retardation of the development of the secondary sex characteristics (2) the finding of an abnormally low 17 ketosteroid excretion and (3) the patient s own concern and apprehension about his small genitalia The clinical manifestations of hypogonadism are obvious in the male Normally one expects the male to go through puberty at 11 to 14 years of

Anterior Pituitary Disturbances

The pituitary conditions which require some type of hormonal therapy follow

Acromegaly —Patients with this condition have enlargement of the pituitary gland due in part to an eosinophilic adenoma The hypertrophy and hyperplasia of the eosinophilic elements may be of such a degree that by the process of compression and pressure alone various other components of the pituitary gland may be destroyed and there may be erosion of the bony components of the sella turcica Therapy for acromegaly is dependent in part on the extent of the condition If the patient shows acromegalic features and has neither significant enlargement of the sella turcica nor visual field constriction one may temporize and utilize the methylated steroids as a means of preventing further pituitary enlargement This is particularly applicable to the male in whom methyltestosterone and/or methandriol may be used with some effectiveness in slowing down the process

The patient should be watched carefully No further therapy besides the oral steroid preparation is indicated unless encroachment of the visual field is noted In such patients and in those in whom considerable enlargement of the sella turcica has also resulted in erosion of the clinoid processes radiation therapy is indicated Radiation therapy does not provide the solution to treatment inasmuch as during the process of radiation postradiation swelling of the elements receiving the therapy may occur resulting in increased limitation of the visual field

It is important for the clinician and radiologist to work closely with the ophthalmologist with visual field examinations being made repeatedly during the process of administering 4 000 to 5 000 roentgens If the visual field is diminished during this treatment by one third of that prior to therapy hypophysectomy should be performed The surgical removal of the pituitary gland of course dooms the patient to persistent hypopituitarism On the other hand some female patients who have had a course of radiation therapy have had regular menstrual periods recur a decade or more after the radiation therapy was discontinued These patients as well as others reported in the literature provide a reason for sparing the scalpel and using less strenuous techniques especially in patients desiring to retain reproductive function

Acromegalic patients in whom pituitary destruction has occurred as a result of pressure necrosis and/or radiation should be treated precisely the same way as the panhypopituitary patient There has been evidence of some damage to the brain in patients receiving inappropriate radiation therapy With the modern approach to radiation techniques such sequelae are less prone to occur

Craniopharyngioma —This pituitary abnormality usually occurs in the younger age group and may be associated with a marked expansion of the sella turcica or the region above the sella turcica so that blindness may result from the pressure on the optic chiasma Radiation in these patients may be of no avail They may require surgical removal of the cyst and the neoplastic process Obviously such patients will then suffer from panhypopituitarism and require replacement therapy

Chromophobic Tumor —Although there are four types of pituitary cells it has been said that the chromophobic cells are the parent or stem cells which give

fertility is desired may result in the formation of anti A and B factors in the body because of the presence of blood grouping factors in the combined urine extract obtained from many pregnant women As a result HCG may produce a hematologic picture comparable to that seen in RH negative mothers in whom an anti RH titer has developed during pregnancy This possibility in an infertile patient desiring cyesis might adversely affect her conception even if infertility is successfully treated

GONADAL FAILURE IN THE FEMALE—The chorionic gonadotropic hormone prepared from the serum of pregnant mares (PMS Equinex) is primarily FSH (follicle stimulating hormone) in activity although it does have some degree of luteinizing hormone activity This preparation has been used in both men and women Its use in females because of its powerful follicle stimulating properties may result in the formation of cystic ovaries The use of pregnant mare's serum (PMS) in the female should be relegated to diagnostic procedures alone Injections of 500 I U of PMS 3 times a week for 3 weeks in a female with evidence of ovarian failure may be employed as a diagnostic test to determine the functional capacity of the ovaries If the ovaries are capable of responding the FSH activity of the equine gonadotropin would be effective in inducing an increased estrogen output from the ovaries Evidence of the increased estrogenic production by the ovary would be manifested by maturation of the vaginal smear increased breast tenderness swelling and the occurrence of menses after the PMS is discontinued This technique has been used to determine whether the ovaries of patients with primary or secondary amenorrhea are irrevocably inactive or capable of response

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seminiferous tubules of the testes Patients with oligospermia and a low FSH production from their own pituitary glands may be helped therapeutically by the administration of PMS in doses of 500 I U 3 times a week for 5 to 7 weeks Prolonged administration of PMS may have the inherent danger of production of antigonadotropic hormone since the gonadotropic extract is prepared from sources other than the human being This must be an ever present potential contraindication to the chronic use of PMS Before its use particularly when there is a history of sensitivity to horse protein the patient should either be skin tested or be checked by topical application of the extract on the conjunctiva If a significant reaction occurs the preparation should not be employed in such a patient The use of a highly purified preparation now available (Equinex) has not induced any untoward reaction in the past 5 to 6 years in my experience

PANHYPOPITUITARISM—The use of pituitary hormones in clinical syndromes such as panhypopituitarism is limited by the fact that these preparations must be administered parenterally and all of them except ACTH are prone to induce antihormone formation The inconvenience of administration and the nullification of activity by antihormone formation makes it necessary to resort to end organ replacement therapy using those hormones of the target glands which are normally responsible for maintaining the homeostasis of the body

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rise to the basophilic, eosinophilic, or amphophilic cells Chromophobic aden occur in patients in all decades of life, but patients with these tumors do no spond as well to radiation therapy as does the acromegalic patient As in patient with craniopharyngioma, surgical intervention may be the procedure choice with the resulting panhypopituitarism being treated as described on page 5

Sheehan's Syndrome—This syndrome is one of panhypopituitarism arisi as a result of pituitary thromboses or ischemia usually occurring followi postpartum hemorrhage or excessive blood loss Such a patient is a fema looking somewhat older than her stated age, with absence of pubic and axillar hair without cachexia, so that her breast development remains moderately nor mal The skin is wrinkled and gives the face a wizened appearance All the lab oratory examinations indicate low or absent thyroid, adrenal, and gonadal func tion, as well as absence of pituitary activity Therapy in such patients requires complete replacement treatment with thyroid, adrenal, and gonadal therapy Adrenal therapy usually includes only glucocorticoids for their effects upon car- bohydrate metabolism and combating stress The sodium retaining steroids usu ally are not required but are employed only in those patients with the systolic blood pressure below 100 mm Hg

Chiari-Frommel Syndrome—This syndrome may be a variant of Sheehan's syndrome However, persons with this syndrome do not show the wizened appear ance characteristic of Sheehan's syndrome, but exhibit the amenorrhea associated with acromegalic like facies and persistent lactation The prognosis with respect to fertility as in those with Sheehan's syndrome is hopeless However, with gonadal-replacement therapy alone these patients do splendidly

A characteristic of this syndrome is galactorrhea, which is usually not very responsive to suppressive doses of the sex steroids It will however diminish in sufficient degree to make the patient more comfortable and less troubled with soiled lingerie The use of the 19 norsteroids with estrogen will diminish the galactorrhea and at the same time induce menstrual periods at periodic intervals for as long as the patient is on steroid therapy Spontaneous resumption of periods cannot be expected However when therapy is discontinued after a year or two of persistent treatment the galactorrhea may return, but it will be markedly less than that initially

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Pituitary Dwarfism—Patients with pituitary dwarfism show a defect in wth, but are without evidence of any other endocrinopathy It is presumed

Anterior Pituitary Disturbances

The pituitary conditions *which require some type of hormonal therapy* follow

Acromegaly —Patients with this condition have enlargement of the pituitary gland due, in part, to an eosinophilic adenoma The hypertrophy and hyperplasia of the eosinophilic elements may be of such a degree that, by the process of compression and pressure alone various other components of the pituitary gland may be destroyed and there may be erosion of the bony components of the sella turcica *Therapy for acromegaly is dependent, in part, on the extent of the condition* If the patient shows acromegalic features and has neither significant enlargement of the sella turcica nor visual field constriction, one may temporize and utilize the methylated steroids as a means of preventing further pituitary enlargement This is particularly applicable to the male, in whom methyltestosterone and/or methandriol may be used with some effectiveness in slowing down the process

The patient should be watched carefully No further therapy besides the *oral steroid preparation is indicated unless encroachment of the visual field is noted* In such patients and in those in whom considerable enlargement of the sella turcica has also resulted in erosion of the clinoid processes, radiation therapy is indicated Radiation therapy does not provide the solution to treatment, inasmuch as during the process of radiation, postradiation swelling of the elements receiving the therapy may occur, resulting in increased limitation of the visual field

It is important for the clinician and radiologist to work closely with the *ophthalmologist with visual field examinations being made repeatedly* during the process of administering 4,000 to 5,000 roentgens If the visual field is diminished during this treatment by one third of that prior to therapy, hypophysectomy should be performed The surgical removal of the pituitary gland, of course, dooms the patient to persistent hypopituitarism On the other hand some female patients, who have had a course of radiation therapy, have had regular menstrual periods recur a decade or more after the radiation therapy was discontinued These patients as well as others reported in the literature, provide a reason for sparing the scalpel and using less strenuous techniques, especially in patients desiring to retain reproductive function

Acromegalic patients in whom pituitary destruction has occurred as a result of pressure necrosis and/or radiation, should be treated precisely the same way as the panhypopituitary patient *There has been evidence of some damage to the brain in patients receiving inappropriate radiation therapy* With the modern approach to radiation techniques such sequelae are less prone to occur

Craniopharyngioma —This pituitary abnormality usually occurs in the younger age group and may be associated with a marked expansion of the sella turcica or the region above the sella turcica, so that blindness may result from the pressure on the optic chiasma Radiation in these patients may be of no avail They may require *surgical removal of the cyst* and the neoplastic process Obviously, such

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rise to the basophilic, eosinophilic, or amphophilic cells Chromophobic adenomas occur in patients in all decades of life, but patients with these tumors do not respond as well to radiation therapy as does the acromegalic patient As in the patient with craniopharyngioma surgical intervention may be the procedure of choice with the resulting panhypopituitarism being treated as described on page 561

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Pituitary Dwarfism—Patients with pituitary dwarfism show a defect in growth, but are without evidence of any other endocrinopathy It is presumed

that these persons may have a selective insufficiency of the eosinophilic cells similar to that seen in certain dwarfed strains of mice

Specific therapy requires the administration of pituitary growth hormone, preferably that from either human beings or monkeys The use of such a preparation would not be conducive to the formation of antihormone and consequently would not result in decreasing effectiveness as therapy is continued The prognosis with respect to reproduction and other activities is good If growth can be achieved with growth hormone, a comparatively normal physiologic reproductive state would be assured

Of course the panhypopituitary dwarf could never be expected to achieve normal functions and would, of necessity, have to be maintained upon complete replacement therapy similar to that advocated for patients with panhypopituitarism in the adult stage

Gigantism —Gigantism is as distressing as dwarfism to the person affected The prevention of gigantism, however, can be relatively simple if early diagnosis is made In contrast to the poor prognosis with respect to increasing height in patients with pituitary dwarfism some assurance of effectiveness of therapy can be given the parents of the excessively tall child The use of steroid hormones to close the epiphyses of probable giants is the procedure of choice Both estrogen and testosterone can be readily employed in either sex with a predominance of estrogen being used in the female and testosterone in the male The question arises whether such steroid hormone therapy would have an adverse effect upon the future reproductive potential Fortunately there is a physiologic analogy between the effect of excessive sex steroids secreted early in life upon genital function and patients with congenital adrenogenital syndrome The latter, as will be discussed later are subjected to unusually large amounts of sex steroids from their prenatal period on Nevertheless at any stage in life—at the age of 10, 20 or 30 years—when placed upon appropriate corticoid therapy, these patients begin to function normally as far as reproductive activity is concerned These data indicate that prolonged and excessive sex steroid effects early in life do not have a deleterious effect upon later gonadal function

TREATMENT —The following therapeutic approach to gigantism in the female is advised oral administration of 2 5 mg of conjugated equine estrogens or 0 1 mg of ethinyl estradiol twice daily for a continuous period of 6 to 12 months at 4 to 5 week intervals a weekly course of therapy with norethynodrel (Enovid) or norethindrone (Norlutin), 10 mg 3 times a day, or 2 5 mg 3 times a day of medroxyprogesterone acetate (Provera)

The purpose of these 19 norsteroids is to induce secretory changes in the endometrium so that the resulting catamenia will prevent endometrial hyperplasia. The progestational therapy achieves a medical curettage, preventing excessive uterine stimulation and inducing menstrual bleeding according to plan Without such therapy cystic glandular hyperplasia of the endometrium may result, eventually causing excessive and abnormal uterine bleeding

If oral therapy is difficult, the patient may then be given 10 mg of estradiol cyclopentylpropionate (Depo Estradiol) or 20 mg of estradiol valerate (Delestrogen) at 10 day intervals, together with the oral 19 norsteroid therapy as recom

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mended previously To potentiate the effect of estrogen upon the epiphyses, 10 mg of methyltestosterone twice daily may be added to the above regimen and continued for as long a time as is necessary unless acne intervenes The epiphyses of these patients should be studied at 4-month intervals, and, if closure is imminent, further steroid therapy can be discontinued

Treatment in the male with gigantism also requires the use of estrogen because estrogen is by far the most effective agent in accelerating premature closure of the epiphyses The parenteral therapy of choice is as follows 10 mg of estradiol cyclopentylpropionate or 20 mg of estradiol valerate intramuscularly every 2 to 3 weeks, plus 100 mg of testosterone cyclopentylpropionate (Depo-Testosterone) at the same intervals The patient will develop some evidence of gynecomastia and breast tenderness which will usually disappear at the cessation of therapy and may even become less evident while the steroid therapy is being continued When epiphyseal closure is obvious such therapy may be discontinued It is gratifying to be able to arrest excessive growth so easily, thereby changing a potentially grotesque person into a normal one

Prior to the initiation of any steroid hormone therapy for the purpose of inducing epiphyseal closure it is important of course to examine the sella turcica and make sure that there is no evidence of pituitary tumor In cases of suspicious enlargement of the sella turcica or if the patient complains of loss of visual acuity visual field studies should also be examined If they are abnormal appropriate therapy should be initiated as outlined for treatment of acromegaly

Posterior Pituitary Hormone Defects

Diabetes Insipidus—The primary disease concerned with disturbances of posterior pituitary hormone is diabetes insipidus Either as a result of a neurogenic lesion in the area of the hypothalamus above the posterior lobe of the pituitary gland or of disease in the posterior lobe itself, inadequate amounts of antidiuretic hormone are elaborated The absence of this hormone may be of such a degree that the patient may excrete tremendous amounts of urine, thereby requiring excessive ingestion of water to prevent serious dehydration

Therapy for such patients involves the use of posterior pituitary hormone This may be administered in a number of different ways The topical use of a powder by nasal insufflation may give very effective control in those who do not develop nasal sensitivity to the powder It is usual to advise the patient to insufflate the material into his nose every time he urinates In so doing the more he urinates the more powder he takes, resulting in eventual control of urinary frequency thereby requiring less frequent insufflation of the powder This has been an excellent device for controlling urination in most patients with diabetes insipidus Because of its self regulatory features overdosage with posterior pituitary powder is most unlikely If the powder cannot be tolerated, the patient may take the posterior pituitary hormone by injection in the form of Pitressin Tannate in oil The usual dose required is 5 units (1 ml) intramuscularly every 2 to 3 days Occasionally some patients require more and some less frequent administration The use of the aqueous preparations has no place in the therapy of diabetes

Sodium Levothyroxine (Synthroid) Sodium levothyroxine is a crystalline preparation chemically pure, which has the advantages of being reproducible in preparation and manufacture and not dependent on biological assays for standardization It does not deteriorate with age and maintains its effectiveness on the shelf when exposed to a normal degree of moisture

Liothyronine (Cytomel) This crystalline compound presumably is the pure thyroid hormone in the form utilized at the tissue level l triiodothyronine It has the reproducibility of sodium levothyroxine and none of the disadvantages of the crude biological products It is not affected by storage or aging It theoretically is the drug of choice in those patients with the hypometabolic syndrome

General Considerations The thyroid preparations listed above can be characterized with respect to their duration of effect dissipation of activity, and comparative activity Thyroid extract thyroglobulin, and sodium levothyroxine take 2 to 3 weeks to achieve their full effect and consequently require 2 to 3 weeks to be completely dissipated It is unwise therefore to alter the dose of thyroid any more frequently than every 2 to 3 weeks with these preparations since cumulative effects with subsequent toxicity may develop It is also obvious that a dose of thyroid taken before sleep will not disturb the patient s sleep that night but may do so 2 to 3 weeks later In contrast, l triiodothyronine achieves its full effect within 2 to 3 days and is as rapidly dissipated The comparable dose relationship between these thyroid preparations is listed in Table 40

Table 40 Comparative Activity of Different Thyroid Preparations

Product	Average Maintenance Dose in Mg
Thyroid Extract	100
Thyroglobulin	100
Na levothyroxine	0 3 (300γ)
Liothyronine	0 1 (100γ)

dl Triiodothyronine (Trion [illegible]
(liothyronine) inasmuch as its [illegible]
more evanescent, and the response less predictable [illegible] tion is as desirable as the levo form While theoretically the *dl* form of a chemically pure preparation is one half as active as the levo form the *dl* form would contain only a fraction of the levo form if the levo form is the active preparation and the *dl* form is not readily changed into its levo configuration

While the actions of the above preparations particularly the first three take 2 to 3 weeks to develop their full effects it should be noted that their effect upon kidney function is more prompt and rapid The peculiar effect of thyroid in increasing renal blood flow and glomerular filtration will be promptly noted in the responsive patient by a diuresis that may occur shortly after the thyroid material has been ingested often in 24 hours It is, of course unnecessary to administer any of the above thyroid preparations in divided daily dosage A single dose may be taken at any time of the day

Thyroid preparations will achieve their most dramatic and important effect in patients with congenital cretinism It is important that the diagnosis be made

thyroid function There are also other supportive laboratory data, substantiating the clinical evidence of decreased thyroid function, viz, an elevated cholesterol, a flat glucose tolerance curve, and a low BMR. Dryness of the skin, loss of cephalic hair, intolerance to cold, constipation muscle pains and aches, and a slow rebound of the patella reflex are the usual classical signs anticipated in decreased thyroid function

The laboratory evaluation of thyroid disease achieves its greatest usefulness in hypothyroidism We feel that no single parameter should be relied upon to establish the diagnosis Cholesterol values may be a valuable index of thyroid function when the procedure is done well and studied with respect to response to therapy The glucose tolerance test is a valuable adjunct in diagnosing aberrations of thyroid function This is based in part upon the property of thyroid hormone to increase phosphorylization Consequently, carbohydrate absorption from the intestinal tract may be normal, depressed, or accelerated, depending upon whether the patient is euthyroid, hypothyroid or hyperthyroid When the tests listed above are evaluated in conjunction with the basal metabolism test, radioactive iodine studies, and protein bound iodine test, a complete picture of the thyroid status and diagnosis of hypothyroidism, hyperthyroidism, hypometabolism, or euthyroidism can be established

Therapeutic Agents —The therapeutic approach to the treatment of hypothyroidism is of course the use of specific hormonal products There are four such compounds on the market at the present time

Thyroid Extract This compound is the original preparation made available for clinical use and is standardized purely on the basis that the extract has an appropriate percentage of iodine, namely 0 2 per cent There are no other specific criteria that must be met Consequently an unusual degree of variability may be noted in a patient's response to thyroid extracts made in different commercial houses Thyroid extract obtained from the gland of a cow killed in Texas, while having the same iodine content per gram as that from a cow killed in Chicago would not necessarily have the same physiologic activity It must be emphasized that the physiologic activity of any one preparation is not dependent solely upon its iodine content The activity of the extract is affected by the nutritional state and the endocrine status of the animal from which the gland has been obtained, and the stress to which the animal is exposed prior to slaughtering In addition, the longer the preparation stays on the pharmacist's shelf the more likelihood there is that there will be a diminution of activity This loss is markedly accelerated in the material stored in moist areas

Thyroglobulin This preparation represents some attempt of purification and is prepared so that 1 mg is equal in activity to 1 mg of U S P thyroid extract In addition the iodine content of thyroglobulin is precisely the same as that of thyroid extract, namely, 0 2 per cent Thyroglobulin however is a more precise preparation than U S P thyroid in that the preparation is biologically assayed in thyroidectomized animals This provides a double set of standards and removes the variability noted with U S P thyroid itself However while all lots are biologically comparable when freshly prepared, they also deteriorate with age and upon exposure to moisture

Once the diagnosis is made, the therapeutic approach, of course, is surgical removal of the parathyroid glands, which may be adenomatous in character Unfortunately, many times it is difficult to locate the adenoma and, despite the diagnosis surgical evidence of the disease may be lacking In these patients it is important to limit the intake of calcium The use of sodium phytate, in doses of 8 Gm per day may be effective in diminishing the absorption of calcium from the intestinal tract This, of course may be of value in patients in whom surgical demonstration of the disease was not possible After the removal of the parathyroid adenoma the patient may go into a temporary phase of hypoparathyroidism Here the intravenous use of calcium gluconate may prevent tetany or arrest it The material may be administered intravenously, slowly and with caution in doses of 0 5 Gm Obviously a patient also receiving digitalis should receive calcium salts very cautiously to avoid serious cardiac arrhythmias

THE ADRENAL GLANDS

Therapy directed toward abnormalities of adrenal function is principally concerned with disease of the cortex While the medulla is an integral part of the adrenal gland there is little in the way of medical therapy that may be utilized in a disturbance of function of the medulla

Adrenal Medulla

The only abnormality of medullary function which can be recognized and corrected is that of hyperactivity seen in patients with a pheochromocytoma In such patients therapy is primarily surgery however medical means must usually be employed to establish the correct diagnosis The drugs most commonly used in the diagnostic procedures are those which induce a provocative response in normotensive phases or lysis of blood pressure during the periods of active over activity The provocative drugs which have been most effective are histamine and methacholine Their mechanism of action is primarily to induce a sympathomimetic overplay, either directly by stimulation of the medullary tissue or extra adrenal chromaffin tissue, or indirectly by visceral vasodilatation whereby the reduction in blood pressure so induced acts as a stimulus for secretion of epinephrine from the adrenal medullary or chromaffin tissue In the presence of a pheochromocytoma an exaggerated increase in blood pressure will occur In patients in whom hypertension is present, lysis of the blood pressure may be achieved by the use of phentolamine (Regitine) or benzodioxane Phentolamine is the drug of choice inasmuch as it may be administered either intramuscularly, intravenously or subcutaneously in doses of 5 mg to induce lysis of the blood pressure in most patients with an active phase of pheochromocytoma When hypertension of sufficient magnitude is induced with the provocative drugs, lysis of the blood pressure may be accomplished with these drugs thereby offering substantiation of the diagnosis

Chemical tests for … of increased catecholamine excretion in the urine may eventually replace … c procedures previously described Biological tests for … of … like substances in the urine, utilizing special

early In addition to the laboratory criteria, a study of the bone age may be of utmost importance in establishing the diagnosis of cretinism or severe hypothyroidism The presence of fine lanugo-like hair growth is also an important pathognomonic sign of hypothyroidism in infants or children It is in these patients that one can achieve a splendid effect, provided the thyroid dose is pushed to tolerance

The best criterion for determining tolerance to thyroid is the effect on the child's pulse while asleep It is as important a criterion for determining maximum tolerance of dosage as we have The normal pulse of a sleeping child below the age of 1 year may range between 90 and 100 That of a child above 1 year of age may range from 90 down, depending upon the age of the child A parent who takes the pulse accurately serves his physician well in helping him determine the dose best suited for the patient An important rule of thumb in thyroid therapy is that the markedly hypothyroid patient is much more sensitive to thyroid drugs than is the euthyroid or hyperthyroid individual One should note that initial thyroid medication may change the long standing cretin from a jocular, chirpy, happy person to one who is morose belligerent and difficult to handle These personality changes must be considered in the decision of whether to institute therapy in the long standing cretin since therapy at that time will have little effect on the mental retardation or ravages of the primary disease

Hyperthyroidism —The treatment of hyperthyroidism has encompassed three major forms of diverse therapeutic approaches—surgery, radioactive iodine, and antithyroid therapy In a chapter on the use of drugs in different disease entities it is, of course important that the medical management of a syndrome be emphasized In general the medical control of hyperthyroidism has been relegated to the background because of the rapidity of results achieved with surgical treatment and the convenience of radioactive iodine therapy There is no question that in the elderly thyrotoxic cardiac patient the use of radioactive iodine (RAI) is the most propitious form of therapy Similarly the surgical removal of a toxic gland, so enlarged that pressure upon the esophagus and adjacent structure leads to discomfort as well as to an unaesthetic appearance, is no doubt the procedure of choice

The use of RAI in patients below the age of 30 or 35 years should be questioned because of the potential neoplastic effects in the thyroid glands of these patients, particularly 2 to 3 decades after the RAI has been administered Similarly, the increasing incidence of nodularity in the thyroid gland of children who have received RAI for hyperthyroidism in the past makes such a procedure seem undesirable The surgical management of the thyrotoxic gland in a patient showing no evidence of nodularity and in whom the gland is not grotesquely enlarged appears to be unwarranted in view of the anticipated good results in cooperative patients following appropriate medical management in the manner described below

TREATMENT —The medical management of hyperthyroidism is the procedure of choice in patients with exophthalmos who also have a marked phobia against any surgical procedure The use of the antithyroid drugs in these persons must be for an extended period of time, with adequate safeguards set up to prevent untoward toxic effects or undesirable side effects of consequence Propylthiouracil

Once the diagnosis is made, the therapeutic approach, of course, is surgical removal of the parathyroid glands, which may be adenomatous in character Unfortunately, many times it is difficult to locate the adenoma and, despite the diagnosis surgical evidence of the disease may be lacking In these patients it is important to limit the intake of calcium The use of sodium phytate, in doses of 8 Gm per day, may be effective in diminishing the absorption of calcium from the intestinal tract This, of course, may be of value in patients in whom surgical demonstration of the disease was not possible After the removal of the parathyroid adenoma, the patient may go into a temporary phase of hypoparathyroidism Here the intravenous use of calcium gluconate may prevent tetany or arrest it The material may be administered intravenously, slowly and with caution in doses of 0 5 Gm Obviously, a patient also receiving digitalis should receive calcium salts very cautiously to avoid serious cardiac arrhythmias

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Chemical tests for detection of increased catecholamine excretion in the urine may eventually replace the diagnostic procedures previously described Biological tests for detection of norepinephrine like substances in the urine, utilizing special

artery sections obtained from the rabbit dorsal aorta, have been described Significant in vitro contraction of the aorta strip will occur with the addition of norepinephrine or urine from a patient with a pheochromocytoma When diagnosis is definitely established by provocative tests, lytic drugs, chemical isolation, or biologic procedures, surgical ablation of the tumor is necessary In this procedure the use of phentolamine may be helpful in preventing serious or fatal hypertensive crisis which may occur during the manipulation of the tumor

Adrenal Cortex

The adrenal cortex, having a multiplicity of functions, may produce a multiplicity of diseases In understanding the therapeutic approach to diseases of the adrenal cortex one must comprehend the interrelationship between the pituitary gland and the adrenal glands The adrenal cortex is not entirely controlled by pituitary ACTH The adrenocorticotropic hormone stimulates primarily the two innermost zone layers of the adrenal cortex, namely, the zona fasciculata and the zona reticularis The zona glomerulosa, the third and outermost zone layer of the adrenal cortex, is not under pituitary ACTH control The steroid produced by the zona glomerulosa is aldosterone

Aldosterone—Aldosterone is primarily concerned with the control of water and electrolyte metabolism its secretion being influenced by electrolytes and the degree of hydration which it itself controls, either directly or indirectly via the diencephalon The stimulus for aldosterone secretion is low sodium, high potassium level, or dehydration Aldosterone secretion is inhibited by high sodium, low potassium, or overhydration The clinical use of aldosterone is limited not only by its cost and relative unavailability, but also by the fact that it must be administered intramuscularly Inasmuch as other synthetic steroids are much more effective orally in inducing sodium retention, they are the drugs of choice in the treatment of the electrolyte disturbance associated with adrenal insufficiency or Addison's disease

Other Cortical Hormones—Of the two innermost zone layers of the adrenal cortex the zona fasciculata, the middle zone layer, is concerned with the formation and elaboration of hydrocortisone Hydrocortisone under the stimulus of ACTH from the pituitary gland is formed from cholesterol taken up by the zona fasciculata from the blood stream Cholesterol is converted in stepwise progression to pregnenolone, progesterone, 17-hydroxyprogesterone, Compound S, and finally to hydrocortisone This is an orderly process with the end products, Compound S and hydrocortisone, being formed by the process of hydroxylation at C 21 and C 11 so that 17-hydroxyprogesterone is converted to hydrocortisone The control of adrenal stimulation by ACTH rests in hydrocortisone itself When the hydrocortisone level reaches a critical point, further ACTH secretion is inhibited or prevented Consequently excessive stimulation of the adrenal cortex by ACTH is controlled as long as adequate production of hydrocortisone is assured ACTH also stimulates the zona reticularis to produce the sex steroids of which the 17-keto steroid precursors are the principal ones The sex steroids are three in number, namely, androgens (17 ketosteroid precursors), estrogens, and progestogens The

androgens and the estrogens have an ever-present potential sex steroid effect when they are present in excessive amounts

Hypoadrenocorticism —Decreased function of the adrenal cortex may be due to primary disease of the adrenal gland itself, or it may be secondary to pituitary ACTH insufficiency The clinical manifestations of Addison's disease are classical and need no emphasis at this time It is important to note, however that the asthenia and fatigue these patients show are perhaps the most important clinical manifestations of adrenal insufficiency In addition to the classical clinical features the diagnosis of adrenal insufficiency also rests upon a finding of low levels of 17 ketosteroids and 17 hydroxysteroids in the urine and a low level of 17 hydroxysteroids in the blood One can differentiate between primary and secondary hypoadrenocorticism by the administration of ACTH, 40 units of the gel will have no effect in increasing the 17 hydroxysteroids in the blood or urine or the urinary 17-ketosteroids in patients with primary adrenal disease Secondary adrenal insufficiency is characterized by an increased excretion of 17 ketosteroids in the urine and 17-hydroxysteroids both in the urine and blood after the administration of ACTH Another important clinical difference is the presence or absence of pigmentation Pigmentation is invariably noted in patients with primary adrenal disease and rarely, if ever, in patients with secondary adrenal insufficiency The inability of patients to excrete water under a water load is another classical finding in Addison's disease which can be readily established in the physician's office by a water-tolerance test

Therapy of Addison's disease is no longer the problem of magnitude it had been in the past Before the days of corticosteroids, excessive salt intake was the only measure for the treatment of adrenal insufficiency In contrast to the ineffectiveness of sodium alone with the advent of crude adrenocortical extracts, patients with adrenal crises could be saved by large doses Unfortunately, these extracts were prohibitively expensive and required frequent daily administration to achieve a therapeutic effect A decided advancement in therapy was made when desoxycorticosterone acetate (DCA) was made available This steroid decreased the difficulties of frequent administration and provided adequate control for most patients with Addison's disease except during a crisis or when the patient was exposed to a stress situation

DCA is available as an oil solution containing 5 mg per milliliter, as a 2 mg Linguet and as a pellet for intramuscular or subcutaneous implantation Although convenient, the use of the Linguet was not predictable The use of the oil solution required injections daily or every 2 days, but assured the patient of adequate control Pellet implantation would last approximately 4 to 6 months and was a very convenient form of therapy, as the pellets could be implanted in the office and were well tolerated The site of implantation may be in either the inguinal or subscapular areas The dose to be implanted is dependent upon the intramuscular daily maintenance dose of DCA in oil Usually one uses one 75 mg pellet for each 0 25 mg of DCA required per day

The preparations listed above however, must now be considered as being largely of historical interest since the following two modes of therapy have been

artery sections obtained from the rabbit dorsal aorta have been described Significant in vitro contraction of the aorta strip will occur with the addition of norepinephrine or urine from a patient with a pheochromocytoma When diagnosis is definitely established by provocative tests lytic drugs chemical isolation or biologic procedures surgical ablation of the tumor is necessary In this procedure the use of phentolamine may be helpful in preventing serious or fatal hypertensive crisis which may occur during the manipulation of the tumor

Adrenal Cortex

The adrenal cortex having a multiplicity of functions may produce a multiplicity of diseases In understanding the therapeutic approach to diseases of the adrenal cortex one must comprehend the interrelationship between the pituitary gland and the adrenal glands The adrenal cortex is not entirely controlled by pituitary ACTH The adrenocorticotropic hormone stimulates primarily the two innermost zone layers of the adrenal cortex namely the zona fasciculata and the zona reticularis The zona glomerulosa the third and outermost zone layer of the adrenal cortex is not under pituitary ACTH control The steroid produced by the zona glomerulosa is aldosterone

Aldosterone—Aldosterone is primarily concerned with the control of water and electrolyte metabolism its secretion being influenced by electrolytes and the degree of hydration which it itself controls either directly or indirectly via the diencephalon The stimulus for aldosterone secretion is low sodium high potassium level or dehydration Aldosterone secretion is inhibited by high sodium low potassium or overhydration The clinical use of aldosterone is limited not only by its cost and relative unavailability but also by the fact that it must be administered intramuscularly Inasmuch as other synthetic steroids are much more effective orally in inducing sodium retention they are the drugs of choice in the treatment of the electrolyte disturbance associated with adrenal insufficiency or Addison s disease

Other Cortical Hormones.—Of the two innermost zone layers of the adrenal cortex the zona fasciculata the middle zone layer is concerned with the formation and elaboration of hydrocortisone Hydrocortisone under the stimulus of ACTH from the pituitary gland is formed from cholesterol taken up by the zona fasciculata from the blood stream Cholesterol is converted in stepwise progression to pregnenolone progesterone 17 hydroxyprogesterone Compound S and finally to hydrocortisone This is an orderly process with the end products Compound S and hydrocortisone being formed by the process of hydroxylation at C 21 and C 11 so that 17 hydroxyprogesterone is converted to hydrocortisone The control of adrenal stimulation by ACTH rests in hydrocortisone itself When the hydrocortisone level reaches a critical point further ACTH secretion is inhibited or prevented Consequently excessive stimulation of the adrenal cortex by ACTH is controlled as long as adequate production of hydrocortisone is assured ACTH also stimulates the zona reticularis to produce the sex steroids of which the 17 ketosteroid precursors are the principal ones The sex steroids are three in number namely androgens (17 ketosteroid precursors) estrogens and progestogens The

CUSHING S SYNDROME The diagnosis of Cushing s syndrome may be made upon the classical clinical findings which need *no further description here* In most instances however confirmation by laboratory data such as decreased glucose tolerance, occasionally insulin resistance, normal or low 17 ketosteroids, *elevated* 17 hydroxysteroids in the urine and blood, and marked increase in blood and urinary 17 hydroxysteroids after a provocative ACTH test is required In the intravenous or intramuscular provocative ACTH test urine and blood are collected before and after the injection of ACTH as previously described Blood and urinary 17 hydroxysteroid values above 50 gammas per 100 ml or 50 mg per 24 hours respectively, after ACTH administration are indicative of Cushing s syndrome

In such patients bilateral total adrenalectomy is the procedure of choice The *preoperative management of these* patients requires the use of cortisone the day before surgery and the day of surgery in doses of 50 to 100 mg intramuscularly During the surgical procedure the *patient receives 100 mg of hydrocortisone intravenously* Following surgery cortisone is administered in the range of 50 mg 3 or 4 *times daily for 3 days followed by gradual reduction* of the dose so that at the end of a week the patient can be maintained orally on 25 to 30 mg of hydrocortisone per day If at any time the patient shows significant adrenal insufficiency intravenous administration of hydrocortisone hemisuccinate is the drug of choice during the phase of acute insufficiency, followed by repetition of the initial doses of cortisone used postoperatively It is imperative to note that in the treatment of any patient with large doses of corticoids plus sodium marked potassium depletion may occur This may result in *loss* of tissue potassium *sufficient* to induce some signs of cardiac irregularities Potassium supplementation with orange juice *and 10 to 20 ml of Kaon per day would prevent untoward reactions due to the* hypokalemia

The management of patients after adrenalectomy is precisely the same as that in patients with hypoadrenocorticism In such patients who have hypertension which is sustained after the adrenalectomy there is little need for the sodium retaining corticoids which are used only when significant hypotension develops Pigmentation may appear shortly after adrenalectomy but can usually be ameliorated by the administration of the glucocorticoids The sodium retaining corticoids in doses adequate for the control of electrolyte metabolism are less effective in preventing or inhibiting pigmentation *The adrenalectomized patient is markedly* sensitive to hypotensive drugs so that while reserpine may be very effective in *reducing blood pressure elevation* maintained after adrenalectomy caution is advised with the use of any antihypertensive agent in the adrenalectomized patients

HYPERADRENOCORTICISM WITH ADRENOGENITALISM —Hyperadrenocorticism concerned with the adrenogenital syndrome is an entirely different clinical entity from that of Cushing s syndrome Females with the adrenogenital syndrome are usually masculinized while in males the external genitalia except for the testes are unusually well developed This syndrome has been ascribed to a metabolic disturbance in the zona fasciculata whereby *hydroxylation is interfered with* The process of hydroxylation is essential to complete the stepwise progression of steroid synthesis *in the orderly progression* from cholesterol to hydrocortisone

ınd to be decidedly more convenient and acceptable to both the patient and the ysician Addison's disease may now be controlled parenterally by the use of the ıg acting desoxycorticosterone triphenylacetate (DCTPA) This preparation is aqueous suspension containing 25 mg per milliliter The usual dose is 1 5 ml 7 5 mg) every 4 to 5 weeks All patients with Addison's disease can be satis torily managed orally with 10 mg of hydrocortisone twice to three times a day ıs 0 1 mg of 9 alpha fluorohydrocortisone per day The fludrocortisone (9-pha fluorohydrocortisone, Florinef) is used only in those patients in whom hypo ısion is present Hydrocortisone is employed to prevent hypoglycemia and permit the patient to go through stress situations without untoward effects ther glucocorticoids may be substituted in equivalent doses in most patients with mparable therapeutic efficacy

It is important to emphasize that the patient with Addison's disease is un ually sensitive to the sodium retaining qualities of any corticoid There are, ıwever, four cardinal signs of overdosage of fludrocortisone which would give the nician an index to the fact that excessive doses of the salt-retaining steroid are ıng administered The patient will show the following changes with such over-ısage (1) elevation of blood pressure (2) excessive increase in weight, (3) crease in heart size, and (4) dependent edema When these signs of excessive dium retention are noted the administration of 9 alpha fluorohydrocortisone ould be stopped All the symptoms usually subside within 3 to 4 days

It is rare for a patient to need more than 0 1 to 0 15 mg of fludrocortisone per ıy The patient may or may not use supplementary salt intake, depending upon s desire As a rule, adequate use of salt in the preparation of food will supply e patient with a normal amount of sodium Occasionally overdosage with flu-ocortisone will also produce muscle weakness which can be attributed to exces ıe potassium loss Usually this can be treated very effectively and simply by the gestion of potassium in the form of orange juice rather than in the form of oral edication If additional amounts of potassium are still required, this may be anaged without gastrointestinal irritation by the use of a liquid, palatable com nation known as Kaon

Hyperadrenocorticism.—Because of the multiple nature and activity of the lrenal cortex hyperfunction may produce several different disease entities In eased activity of the adrenal cortex resulting in Cushing s syndrome may be tributed in part to overactivity of the zona fasciculata, resulting in increased ydrocortisone production While formerly believed to be due primarily to baso ıilic changes in the pituitary gland in the light of our present knowledge Cush g's syndrome can be attributed in its entirety to overproduction of hydrocorti-ıne The rationale for adrenal rather than pituitary origin follows (1) The sease can be induced with cortisone (2) Basophilic changes in the pituitary and are in all probability due to retrograded changes Cortisone will induce ıuitary basophilism In addition Crooke's cells noted in some cases of pituitary asophilism no doubt represent a cell with degenerative hyaline changes (3) fany patients in whom adrenalectomy has been performed for the classical Cush-ıg s syndrome have failed to show morphologic evidence of increased activity in ıe adrenal gland, yet dramatic clinical cure was achieved despite this

change in 17 ketosteroids during any of the 8 hour periods If there is hyperplasia, significant depression of 17 ketosteroids will occur during the infusion The ovary must also be considered as a site of the neoplasm because adrenal rest tumors of the ovary may simulate the adrenogenital syndrome Obviously, when the diagnosis of neoplasia is made, the therapy consists of removal of the neoplasm either from the adrenal cortex or the ovary

THE GONADS

Female*

The treatment of gonadal dysfunction in the female usually revolves around the management of menstrual abnormalities, the use of hormones in the climacteric, and related conditions The menarche normally occurs between the ages of 10 and 14 years Occurrence of the menarche before the age of 10 years may be considered as precocious and after the age of 14 years as delayed The development of the female is usually progressive, the thelarche is followed by the pubarche and then by the menarche

Sexual Precocity —Precocious sexual maturity in the female child warrants attention It is imperative that possible organic pathologic causes be ruled out before a diagnosis of constitutional sexual precocity is made If this diagnosis is made, it is important that precautionary measures be taken to prevent pregnancy These children readily succumb to the advances of sexual deviates because of their inadequate intellectual development The growth problem in these children is also important While in the early stages of their syndrome their height far exceeds the stature of those in their age group, the over-all height of these patients is considerably less than that of the average adult The reason for this is that the steroid hormones cause growth by stimulating the epiphyseal centers, but at the same time, unlike the growth hormone, cause premature epiphyseal closure

These patients should be given gonadotropic hormone prepared from the pituitary glands of animals One may employ hog sheep, or beef pituitary gonadotropic extracts in doses of 25 rat units 3 times a week Therapy must be continued for as long a time as endogenous gonadotropic inhibition is desired While this treatment may sound paradoxical, it is effective in inducing antihormone formation As a result, the antigonadotropic hormone will inhibit the endogenous secretion of gonadotropic hormone by the patient's pituitary gland, thereby producing temporary cessation of gonadal function, and epiphyseal closure will be delayed

Amenorrhea and Delayed Menstruation —Delay in onset of menstruation and primary or secondary amenorrhea may be effectively treated, provided that a correct diagnosis is made It is necessary to rule out disorders of the thyroid or the adrenal glands before attempting to identify which component of the pituitary-ovarian uterine axis is responsible for failure of menstruation

In patients with amenorrhea due to supratentorial or hypothalamic factors, monthly administration of progestational steroids, either as progesterone, 100 mg in

*[Many of these problems are also discussed in Chapter 36 Ed]

When hydroxylation is incomplete, inadequate amounts of Compound S and hydrocortisone are produced As a result, inhibition of pituitary ACTH by hydrocortisone does not take place so that increased ACTH elaboration occurs Inasmuch as ACTH also stimulates the zona reticularis to produce the 17 ketosteroid precursors, a marked increase in 17 ketosteroid excretion is usually noted 17-Hydroxyprogesterone, the steroid which is not completely converted to Compound S, is excreted as pregnanetriol Since elevated levels of 17-hydroxyprogesterone occur in this syndrome, elevated pregnanetriol excretion takes place

The therapy of this syndrome in cases of hyperplasia demands the appropriate use of corticoids The following corticoids may be employed with their comparative doses administered 3 times a day cortisone, 12 5 mg, hydrocortisone, 10 mg prednisone or prednisolone, 2 5 mg methylprednisolone (Medrol), 2 mg, triamcinolone (Aristocort, Kenacort), 2 to 3 mg, and dexamethasone (Decadron, Deronil, Gammacorten), 0 375 mg When these doses are used there is no need to restrict the dietary intake of salt or to add potassium No special dietary restrictions are necessary in the management of the patient The effectiveness of therapy is judged by the level of 17-ketosteroids and/or pregnanetriol excretion In the postpubertal adrenogenital syndrome medication may be stopped, and if elevation of the 17 ketosteroids and pregnanetriol does not occur, there is little need to reinstitute it The patient with congenital adrenocortical hyperplasia, however, must be maintained on corticoids indefinitely When pregnancy occurs in patients with adrenocortical hyperplasia, the need to continue corticoid therapy is questionable because the placenta apparently takes over corticoid function and activity effectively

Adrenogenital Syndrome in the Newborn Infant —The newborn infant with the adrenogenital syndrome may occasionally have a salt-losing syndrome It was first believed that this might be due, in part, to a specific steroid producing excretion of sodium However, in the light of our recent knowledge, infants with the salt losing syndrome no doubt have a complete blockage of hydroxylation which prevents the formation of hydrocortisone However, aldosterone is present at normal levels In the absence of hydrocortisone, aldosterone cannot maintain its sodium-sparing effect The addition of corticoids promptly corrects this abnormality of electrolyte metabolism and permits endogenous aldosterone to effect a sodium-sparing effect Doses of corticoids to be used in these infants are essentially the same as those suggested previously Guides to therapy may also be based upon urinary 17-ketosteroid and pregnanetriol levels

If there is no depression of elevated 17-ketosteroids and pregnanetriol with oral corticoid therapy, one must suspect neoplasia of the adrenal cortex or ovary Normally, individuals with the clinical characteristics of the adrenogenital syndrome and neoplasia of either the adrenal cortex or ovary will not have increased pregnanetriol excretion The diagnosis of neoplasia may be confirmed by the intravenous administration of 100 mg of hydrocortisone hemisuccinate or 25 mg of either prednisolone hemisuccinate or 6 methyl prednisolone hemisuccinate Urine specimens are collected for 8-hour periods before, during, and after the infusion The infusion of the corticoid is allowed to run for 8 hours using the appropriate dose of the selected steroid If the patient has a neoplasm, there will be no significant

pituitary gland or as a consequence of an inability of the ovary to discharge the ovum because of a thickened capsule A differential diagnosis, as well as a therapeutic induction of ovulation, may be attempted by the intravenous use of 20 mg of conjugated equine estrogens Before this procedure is used one must rule out abnormalities of the thyroid and adrenal glands by the methods discussed on page 566 The patient must also show an adequate proliferative phase as manifested by the occurrence of a menstrual period following the oral or intramuscular administration of progestational steroids If ovulation fails to follow the injection of conjugated equine estrogens, the injection should be repeated for 2 successive menstrual cycles 14 or more days after a spontaneous or progesterone induced period If the patient fails to ovulate after all three injections, the likelihood of a thickened tunica of the ovary must be considered as being responsible for blocking ovulation

In these patients a wedge resection of the ovary may confer fertility and regular menstrual periods upon the patient The rationale for the use of intravenous estrogen is based upon our knowledge of the interrelationship existing between the pituitary and the ovary In the sequential secretion of the gonadotropic hormones, estrogen has a dual effect—inhibition of FSH hormone activity and stimulation of release of luteinizing hormone The latter effect may occur either by direct action on the pituitary gland or by indirect action by way of the hypothalamus, probably on the area between the paraventricular and supraoptic nuclei When ovulation is so induced and pregnancy is desired, the patient should be instructed to have intercourse as frequently as possible after the intravenous injection of conjugated equine estrogens

Uterine Bleeding —While amenorrhea may be a difficult problem to manage, the control of excessive uterine bleeding by appropriate hormonal therapy is also important Excessive bleeding occurring either from the time of the menarche or up to the age of 25 is most commonly associated with anovulatory cycles Excessive uterine bleeding occurring at the time of the climacteric must be investigated to rule out neoplastic disease prior to institution of hormonal therapy As in the younger age group, despite the neoplastic propensities in the older woman, the common cause of the bleeding is also anovulatory cycles Treatment of active bleeding consists of the parenteral use of 25 mg per day each of testosterone propionate and progesterone in oil intramuscularly for 5 days The testosterone is used for hemostasis, presumably by its myotropic effect the progesterone changes the endometrium into a secretory phase so that 'a medical curettage' will be achieved 4 to 5 days after the last injection Bleeding will usually stop after the first or second combined injection and will occur again with the medical curettage This therapy has been efficacious in controlling abnormal uterine bleeding of the anovulatory type and makes it unnecessary to do a dilatation and curettage in young unmarried women, thus sparing them both the physical and psychologic trauma of an unnecessary surgical procedure

The patients who have received the combined testosterone and progesterone injections during the active phase of bleeding thereafter receive only 100 mg of progesterone in oil intramuscularly, or one of the oral progestational steroids in the doses previously recommended for 1 week starting 4 weeks after the first combined injection used during the active phase of bleeding At this time there is no

oil (50 mg per milliliter) intramuscularly, or oral progestational agents, norethynodrel (Enovid) or norethindrone (Norlutin), 10 mg of either twice for 7 days, or 2 5 mg 3 times daily of 6 methyl prednisolone (Provera) for 7 will usually induce a menstrual period within 2 weeks Ethisterone, in doses mg 3 times a day for 7 days, or progesterone in suppository form, 50 mg daily for 7 days, may also induce the same response The use of progestat therapy for 2 to 3 successive months will usually be effective in inducing reg menstrual periods There is a long-acting progestational steroid known as hydroxyprogesterone caproate (Delalutin) which will induce a secretory effect doses of 250 mg administered intramuscularly in oil This preparation may not substituted for progesterone in oil when a rapid or prompt effect is desired

After a diagnosis of ovarian failure has been made by appropriate technique cyclic menstruation should be induced in younger women to maintain adequate de velopment of the secondary sexual characteristics or to induce such development primary ovarian agenesis is present Cyclic menstruation may be induced by the use of either parenteral or oral estrogens—parenterally in the form of estradiol cyclo-pentylpropionate (Depo-Estradiol) or estradiol valerate (Delestrogen), 10 mg of either every 2 weeks, or orally in the form of conjugated estrogens, equine, 1 25 mg ethinyl estradiol, 0 05 mg, chlorotrianisene (Tace), 12 mg, methallenestril (Vallestril), 6 mg, dienestrol 0 5 mg, and stilbestrol, 0 1 mg, all being adminis-tered twice daily, or any other appropriate estrogen in comparable doses for three weeks

These preparations are followed by the progestational agent of choice One should note in the treatment of patients with primary amenorrhea that therapy may be simplified by the estrogen medication being taken continuously, while the progestational steroid is administered at monthly or 5-week intervals It is impor-tant to emphasize here that while aqueous progesterone suspensions are on the market, their use is associated with pain and marked induration at the site of injection Progesterone as an aqueous suspension is the most irritating steroid available Such compounds have no place in the armamentarium of the physician because of the marked tissue reaction and pain they induce

The treatment of secondary amenorrhea may require only the use of progesta-tional steroids Secondary amenorrhea may be due, in part, to a failure of ovu lation to take place In such persons, because of persistent or constant secretion of estrogen, there is insufficient change in estrogen level to induce menstrual bleeding Provided there is an adequate proliferative phase, administration of progesterone by parenteral or oral route will induce a menstrual period The doses of progesterone used intramuscularly or orally are the same as those stated previously This type of therapy may lead to spontaneous regular menstrual periods However, if the patient has blockage of ovulation at the ovarian level, such progestational therapy ould be purely palliative and would have to be administered at regular intervals f every 4 to 6 weeks to prevent excessive building up of the endometrium Pro-sterone therapy would induce periodic desquamation of the endometrium so that ressive bleeding would not occur

Ovulatory failure in patients with menstrual irregularities or with infertility blems may be due either to failure of release of luteinizing horm-

ing all the symptoms of the climacteric deserves *appropriate treatment The most* effective is the use of estrogens alone or in combination with androgens, particularly when vasomotor symptoms are severe and predominant The following doses *of estrogens* have proved to be appropriate in controlling the menopausal syndrome without adverse effects conjugated equine estrogens, 1 25 mg per day, ethinyl estradiol, 0 05 mg per day, chlorotrianisene (Tace), 12 mg per day, dienestrol 0 5 mg per day, methallenestril (Vallestril), 3 mg per day, and stilbestrol, 0 1 mg per day

Androgen *therapy may be effective in enhancing the* response *to* estrogens, and in so doing permits the physician to use less estrogen if undesirable side effects such as breast tenderness, uterine bleeding, etc, develop It is important to emphasize that the androgens will not nullify or neutralize the undesirable side effects of estrogens but, by permitting less steroid to be used, the therapeutic efficacy is maintained with fewer or less intense side effects *Half the* dose *of* estrogens recommended above may be used if 5 mg of methyltestosterone is added to the daily regime Androgens alone will usually not be as effective as the estrogens *alone As a rule 10 mg of methyltestosterone* per day is *the lowest* nonarrheno mimetic dose that can be employed with any therapeutic efficacy Osteoporosis of the menopause will be more effectively ameliorated with estrogens and androgens than with estrogens alone

Frigidity—The use of hormones in correcting deficiency of libido has not been *utilized to its fullest extent Although psychiatrists may deny the role of hormones* in libido in the female there is little doubt that androgens enhance libido in women who have once experienced it The mechanism of action is perhaps based upon the clitoral stimulation achieved by androgens Doses of 10 mg of methyl testosterone per day 100 mg of testosterone cyclopentylpropionate (Depo-Testosterone) or 200 mg of testosterone enanthate (Delatestryl) every 4 weeks will enhance libido in women who have once known libido but now find intercourse a laborious duty Women who have always been frigid cannot be expected to be *helped by hormonal therapy they do require psychiatric treatment* In contrast to the beneficial effect that androgens have upon libido, progesterone tends to diminish it Progesterone suppositories in 25 to 50 mg per day will decrease the libidinous drive

Postpartum Breast Engorgement—The treatment of postpartum breast engorgement with hormonal agents has ranged from a wide variety of oral steroids *to an equal number of parenteral steroids* The most effective form of therapy includes the parenteral use of 5 mg of estradiol cyclopentylpropionate (Depo-*Estradiol) plus 100 mg of testosterone cyclopentyl*propionate (Depo Testosterone) in a single intramuscular injection An alternate preparation is 10 mg of estradiol valerate plus 300 mg of testosterone enanthate intramuscularly These represent simple and efficacious treatments without adverse sequelae *for postpartum breast* engorgement Obviously the neurogenic stimulation of suckling must be held in abeyance fluid restriction as well as breast binders help in diminishing pain engorgement, and discomfort at this time Norethindrone (Norlutin) and norethynodrel (Enovid), in doses of 10 mg 3 times a day for 5 to 7 days, provide an oral means *for controlling postpartum* lactation These compounds may also be used

need for androgens since the patient is not actively bleeding The same progesterone regimen is repeated for 2 more 4 week intervals This will usually result in a high percentage of good results If the patient fails to respond, the possibility of intrauterine disease or excessive bleeding from secretory endometrium must be considered In the former, surgical intervention is necessary In the latter, an intravenous injection of conjugated equine estrogens, 20 mg, is effective in decreasing or stopping the flow This is due in part to the fact that the estrogens enhance the production of prothrombin precursors, thereby facilitating prompt hemostasis

Dysmenorrhea.—The treatment of dysmenorrhea has been an enigma and has resulted in the recommendation of a great variety of procedures for its alleviation Since primary intractable dysmenorrhea has been found to be associated with ovulatory changes in the endometrium, inhibition of ovulation with steroids or synthetic estrogens has resulted in good results with relief of pain Doses of 1 mg of stilbestrol, 1 25 mg of conjugated equine estrogens, or 0 05 mg of ethinyl estradiol (Estinyl) administered twice a day from the eighth to the twentieth day of a 28 day menstrual cycle, will inhibit ovulation in most cases and thereby relieve pain However, subsequent cycles require larger doses of the estrogen to prevent ovulation from 'breaking through' An alternative method of inhibiting ovulation may be accomplished by the use of the 19 norsteroids (norethindrone or norethynodrel) administering either compound 10 mg twice a day for 10 days, starting 5 days before the anticipated time of ovulation, i e, on the ninth day of a 28 day cycle Unlike the estrogens, there is no break through of ovulation with continued cyclic therapy with the 19 norsteroids This procedure is obviously unphysiologic and is contraindicated in patients with an infertility problem Preovulatory administration of methyltestosterone, 10 mg 3 times a day, or methandriol (methylandrostenediol), 25 mg twice daily for 8 days starting 4 days before the anticipated day of ovulation, will control dysmenorrhea without inhibiting ovulation Aqueous extracts of corpus luteum administered orally have been ineffective in controlling dysmenorrhea Parenteral extracts have been effective but are prohibitively expensive

Premenstrual Molimen.—The common premenstrual complaint of many women is that of premenstrual molimen, characterized by nervousness, irritability, breast tenderness, abdominal bloating and weight gain Indeed many women show personality changes at this time to such a degree that some penal authorities claim that most of the crimes committed by women take place during this premenstrual state Beyond the use of the usual diuretics, if the patient has dysmenorrhea the preovulatory administration of methyltestosterone or methandriol will be exceedingly effective in combating the premenstrual molimen If the patient does not have dysmenorrhea the use of 10 mg of ethisterone, twice daily for 7 days premenstrually will control most premenstrual symptoms If mastodynia is the primary complaint, the use of methandriol in doses of 30 to 50 mg per day for 7 to 10 days premenstrually will be followed by remarkable improvement

Climacteric.—Many women approaching the menopause or climacteric may be sufficiently uncomfortable or incapacitated to require therapy The treatment of the climacteric may include the use of sedatives, ataractic drugs, estrogens androgens, or estrogens and androgens combined The menopausal patient exhibit-

gence when there is a change of pasture Fortunately, there are several diagnostic procedures that may be performed to uncover any possible endocrine deficiency accounting for diminished libido In these males low 17 ketosteroid and/or elevated gonadotropic (FSH) excretion specifically identify the endocrine nature of the loss of libido and offer promise of improvement with therapy These patients usually respond well to the same doses of androgens recommended previously for hypogonadism The difference is that in long term management, the steroid may be gradually diminished in amount as soon as an adequate therapeutic response is achieved and maintained Therapy may be continued for as long a period of time as necessary, provided that adequate rechecking of the patient is made at frequent enough intervals to detect excessive prostatic hypertrophy In addition patients with hypercholesteremia obviously should have repeated determinations of blood cholesterol to rule out any possible adverse effect which the exogenous androgens might have

One cannot anticipate a satisfactory response of enhanced libido following hormonal therapy in males with normal 17 ketosteroid and FSH excretion

Climacteric.—A discussion of the male climacteric should follow a discussion of libido inasmuch as one of the primary complaints in these patients, in addition to the other symptoms of the climacteric, is the loss of libido and/or potentia This syndrome includes vasomotor symptoms irrationality irritability an inability to concentrate associated with a loss of judgment depression and a loss of ability to get along with people and occasionally suicidal tendencies If these patients also have a high FSH excretion and a low 17 ketosteroid excretion they invariably respond with a considerable degree of improvement to the androgenic regimens advised previously

Gynecomastia—Another problem of major concern in the male is gynecomastia This condition may occur spontaneously at the time of puberty or may follow the use of certain cyclopentenophenanthrene steroid preparations such as estrogens adrenocortical hormones methyltestosterone and cardiac glycosides It may also be seen in elderly patients or in those with hepatic cirrhosis due to alcoholism and occasionally it follows traumatic injury to the breast Gynecomastia may be due to enhanced endogenous production of estrogens from the testes or to an estrogen secreting neoplasm of the adrenal or testes

By and large there is no specific hormonal therapy for idiopathic gynecomastia or that appearing spontaneously in the pubescent male In the majority of these patients it subsides spontaneously When it does not therapy with norethandrolone 10 mg twice or three times a day may be of some help If there is no response after 6 to 8 weeks of this therapy, mammoplasty is the procedure of choice

The use of methyltestosterone is contraindicated in any patient with gynecomastia since it may increase breast size Parenteral androgens are without effect and may also stimulate breast growth in cases in which exogenous androgens may be converted to estrogens Where an etiologic agent may be indicted whether endogenous or exogenous the removal of the cause will usually result in total or marked reduction of the gynecomastia It may never completely disappear in some cases and if this is cosmetically undesirable a mammoplastic procedure would then be the one of choice

in doses of 10 mg twice daily for 15 to 20 days in controlling galactorrhea seen during the menstrual cycle or following pelvic or abdominal surgery

Male

Endocrine problems of the male, while not as diverse or as complex as those *in the female do not often respond to specific therapy as dramatically as in the* female

Hypogonadism—Hypogonadism in the adolescent male has been described and will not be repeated here Hypogonadism in the adult male, when associated with testicular failure, responds dramatically to the administration of the newer longer acting androgenic preparations now available Primary testicular fail[illegible] may occur following bilateral herniorrhaphy as well as surgical procedures f[illegible] orchiopexy It may also be seen as a result of congenital disease of the testes, [illegible] Klinefelter's syndrome or in primary eunuchoidism In both the acquired [illegible] congenital forms of testicular failure the urinary gonadotropic excretion [illegible] variably elevated above the upper limits of normal The prognosis for spo[illegible] restoration of testicular function with respect to androgenic activity, wh[illegible] or for fertility is practically hopeless

In the adult male the use of testosterone cyclopentylpropiona[illegible] Testosterone), testosterone enanthate (Delatestryl), or testosterone ph[illegible] (Perandren Phenylacetate), in doses of 200 mg, 400 mg and 200 mg, [illegible] every 2 to 3 weeks induces an excellent response as far as developme[illegible] sex characteristics and restoration of potency is concerned A[illegible] with primary testicular failure should also receive the same [illegible] Ordinarily, androgens should not be used in the prepubertal or [illegible] unless irreversible testicular failure is evident

The crucial diagnostic test delineating primary from second[illegible] failure is the finding of elevated FSH excretion in the former Th[illegible] adult male with secondary testicular failure due to hypopituitaris[illegible] on chorionic gonadotropin hormone therapy Since this is impract[illegible] the necessity of frequent injections, except in the preadolescent [illegible] therapy previously recommended is also that of choice

Oral therapy with fluoxymesterone (Halotestin Ultandren) [illegible] 10 mg per day is also effective in maintaining a normal andr[illegible] advantage of fluoxymesterone over methyltestosterone is that [illegible] jaundice is presumably less Comparable doses of methyltesto[illegible] 50 mg per day Use of testosterone (never the propionic e[illegible] plantation will give prolonged and smooth therapy Usually nine [illegible] placed in either the right or left inguinal or subscapular areas [illegible] less painful and is not affected by activity However, the skin i[illegible] than that in the inguinal region and is somewhat more difficu[illegible] the trocar The effect lasts about 6 months

Loss of Libido—While many men complain of loss of l[illegible] this is a consequence of endocrine deficiency Psychosomat[illegible] the male are of even greater importance than in the female [illegible] *in the vernacular is that a man who lacks libido with his* [illegible]

ONCLUSIONS

A brief resume of modern concepts of endocrine therapy has been presented he use of the methods described will, in most cases, provide the physician with ome degree of diagnostic acumen and therapeutic success in the treatment of the ommon endocrinopathies As time goes on, no doubt, many of these concepts of ierapy will be altered One must never lose sight of the fact that, while much f the new will replace the old, many of the new hormonal materials provide no eal advantage to anyone but the manufacturers Their great number should not iscourage the physician, but should make him wary and cautious in the lection of an appropriate therapeutic agent The physician should confine him elf to prescribing those selected new compounds which he himself or other ompetent investigators have evaluated

FLECTED REFERENCES

lbright F, Forbes, A D, and Henneman, P H Pseudo pseudohypoparathyroidism Tr

ailer, J

ireiner, 1952

ern, R 57

upperm 2 517, 1957

upperman, H S, and Epstein, J A Endocrine Therapy of Sterility Am Pract & Digest Treat 9 547, 1958

upperman, H S, and Studdiford, W F Endocrine Therapy in Gynecic Disorders Post grad Med 14 410, 1953

upperman, H S, Wetchler, B B, and Blatt, M H G Contemporary Therapy of the

Vilkins and Migeon A J Further Iyperplasia With Cortisone, J

Villiams 1955, W B Saunders Co

Infertility —Occasionally the infertile male with oligospermia will present himself for therapy By and large the therapy of this problem is doomed to failure However in patients with low FSH excretion and low 17 ketosteroid excretion a course of therapy with pregnant mare s serum (Equinex PMS) con sisting of 500 I U 3 times a week for 6 weeks plus biweekly injections of 150 mg of testosterone cyclopentylpropionate (Depo Testosterone) or comparable doses of another long acting androgen will usually significantly increase spermatogenesis and sperm count Unfortunately because of antihormone production this gon adotropic hormone cannot be administered for longer than 6 weeks The androgen however may be continued at 2 to 3 week intervals for as long a period of time as spermatogenesis is maintained at an increased level These doses of androgens will not suppress pituitary gonadotropic function Since androgens maintain spermatogenesis in the hypophysectomized animal they may also have a spermato genic effect in the human being In addition the fact that FSH alone will not maintain or initiate spermatogenesis but requires either ICSH hormone or con comitant androgens points in favor of the use of such doses of androgens in the oligospermic male Methyltestosterone in doses of 25 mg twice a day may be sub stituted and may also be effective not only in oligospermia but also in increasing motility and diminishing the extent of necrospermia

Anabolic Steroids

Anabolic steroids in patients with anorexia nervosa or those with protein depletion associated with debilitating disease have proved to be of some benefit Androgens alone or together with estrogens are certainly excellent protein anabolic steroids However because of the undesirable side effects due to the androgens themselves their use is limited in patients in whom arrhenomimetic effects would be undesirable Several steroids have been recommended because of their potential effect upon protein anabolism without significant androgenicity Whether or not a steroid has selective anabolic activity without androgenicity is still a question There are several preparations on the market which tend to show less androgenicity than does testosterone despite the fact that they are potent anabolic agents These include norethandrolone (Nilevar) and methandriol (Stenediol) both of which may be administered orally and a recent parenteral preparation known as nan drolone phenpropionate (Durabolin) The dose of 10 mg 2 or 3 times a day of the oral anabolic agent has been proved to be of value in producing a positive pro tein balance Norethandrolone because of its progestational activity, may also be administered to females in whom progestational effects are lacking and in whom there may also exist a negative protein balance An adequate progestational effect can be achieved with 10 mg of norethandrolone 3 times a day for 7 days This effect is usually accompanied by some weight gain in patients who previously had a negative protein balance Nandrolone phenpropionate which is structurally norethandrolone plus an ester is said to be effective in producing a positive pro

the compound 2 or 3 times a week

ere may also be used to counteract

They may also be employed in the

treatment of patients with senile osteoporosis

acid The latter preparations possess essentially similar pharmacologic actions and no attempt will be made to differentiate them The anti inflammatory effect is related to the liberation of the salicylate ions although the therapeutic potency of acetylsalicylic acid is considerably greater than that of sodium salicylate Their use is generally advisable orally, and parenteral administration is indicated infrequently and in unusual situations only Analgesia is probably the most sought for therapeutic action of salicylates in the several arthritides Other uses of salicylates, such as for simple headache, nonspecific aches and pains and unidentified viral or bacterial infections of the upper respiratory tract are discussed in other sections of this volume

There are three common rheumatic disorders in which salicylates are of great value These are osteoarthritis rheumatoid arthritis and acute rheumatic fever in order of clinical incidence The therapeutic value is in the reverse order The etiology of osteoarthritis has not been revealed but it is believed to be associated with abnormal or possibly normal wear and tear of joint structures i e, a direct effect of degenerative aging processes rather than the consequences of a specific causative agent Rheumatoid arthritis and acute rheumatic fever, on the other hand, are unanticipated developments in afflicted individuals, and although the etiology of the respective maladies is inadequately defined there are several observations in the literature that suggest etiologic mechanisms Rheumatoid arthritis manifests itself clinically by disseminated articular symptoms, but the disease basically is believed to be a reaction of connective tissue to one or more inciting agents The connective tissue widely distributed throughout the body undergoes change as a consequence of the inciting agent principally in articular, periarticular, and vascular structures Acute rheumatic fever is believed to be an immunologic reaction of cardiac structures and to a lesser degree, of periarticular structures to a hemolytic streptococcal infection

Phenylbutazone —Phenylbutazone (Butazolidin), a congener of aminopyrine and antipyrine has been introduced only recently into clinical medicine The analgesic action is similar to the salicylates in the management of rheumatoid arthritis the uricosuric action is inferior to probenecid Currently this preparation finds its greatest value in the treatment of the acute attack of gouty arthritis although there are a few reports of its employment daily as a *prophylactic in the* intercritical period The incidence of toxicity is responsible for its limited use in patients with rheumatoid arthritis and the need for caution in the daily use of this compound in patients with gout

Colchicine —Colchicine is specific for the alleviation of distress in acute gouty arthritis It has no recognized clinical effect upon other types of acute or chronic joint disease Colchicine is of great value also in the prophylactic management in the intercritical period of the patient moderately or severely afflicted with gouty arthritis Although the precise steps in the intermediary metabolism of uric acid have not been determined most of the experimental evidence suggests that gout is caused by an increased production of uric acid The pathogenesis of the acute articular episode is essentially unknown

Probenecid (Benemid) —This compound was the result of a systematic investigation of a number of selected substances endowed with uricosuric properties

Chapter 32

THE CHOICE OF AN ANTIARTHRITIC AGENT*

John H. Talbott, M D.

INTRODUCTION

This chapter embraces a discussion of the oldest specific pharmacologic agents used in the treatment of arthritic disorders as well as a discussion of selected drugs most recently available Herbs, corms, barks, and other botanicals were the source of the antiquated or traditional preparations, the organic chemical laboratory is the source of the contemporary compounds Infusions containing salicin and methyl salicylate, recovered from willow bark, were known to the ancients as antipyretic nostrums The descendants of these impure preparations, acetylsalicylic acid and sodium salicylate, continue to occupy an enviable position in current clinical practice because of their anti-inflammatory properties The use of colchicum, the predecessor of colchicine and the only specific antiarthritic agent in the pharmacopeia, may be traced to the earliest medical records of Egypt, possibly Greece and India also The Ebers Papyrus, the oldest comprehensive medical text, which was prepared in approximately 1500 B C, is reported to contain a reference to colchicum, an ingredient of several of the species of autumn crocus or meadow saffron Colchicine has not lost its enviable position as an antigout drug The antiarthritic agents prepared most recently include the adrenal steroids, probenecid, and phenylbutazone For most therapeutic purposes, the adrenal steroids and adrenocorticotropin (ACTH) may be considered to be interchangeable The cinchophens and the aminophenols occupy an intermediary position chronologically and a secondary position therapeutically

CLINICAL APPLICATIONS

Salicylates and Pyrazolons —

SALICYLATES —Since salicylic acid is too irritating for internal use, the discussion of this group of agents will be confined to sodium salicylate and acetylsalicylic

*Investigations on gout were supported in part by a Grant in Aid from the National Institutes of Health, Public Health Service, Bethesda, Md

mend ACTH in the selected case of acute gouty arthritis that does not respond to other antigout preparations I agree in each circumstance It is the consensus that a bout of acute rheumatic fever should be treated for several weeks with adrenal steroids or ACTH Finally, almost every physician that is confronted with the management of the unusual collagen disorders, i e, systemic lupus erythemato sus, acute dermatomyositis, systemic scleroderma and polyarteritis, will have no hesitation in recommending one of the steroids for continuous use so long as acute or subacute manifestations of the disease are detected

Gold Salts—Preparations of gold have been used by rheumatologists in the treatment of acute rheumatoid arthritis for more than two decades Historically, gold was recommended in the mistaken belief that rheumatoid arthritis was caused by the tubercle bacillus and gold was indicated in tuberculosis The premise was faulty but the clinical results were noteworthy The mechanism of the action of gold in rheumatoid arthritis is not known Probably it is a mild poison that insults the affected tissues and, for reasons not revealed, alleviation of articular distress follows Toxicity, mild or ominous, is the principal contraindication to its use initially or continually The following gold compounds are available gold sodium thiosulfate, gold sodium thiomalate (Myochrysine), or aurothioglucose (Solganal) The choice of the compound appears to be a personal matter with the physician, although certain advantages support gold sodium thiomalate (Myo chrysine) as the preferred agent

Drugs of Doubtful Utility—It is obvious that the specific items discussed above in no way represent the long list of antiarthritic preparations available cur rently for clinical use Included in this category are vitamin D, sulfonamide prepa rations and antibiotics bee venom, antireticulocytotoxic serum, post partum plasma, para amino benzoic acid, and vaccine, as well as combinations of reliable preparations with substances of doubtful value It is my belief that only those preparations discussed in detail under the appropriate headings merit clinical use, also that combinations of substances of proved value are less desirable than individual prepa rations

GENERAL PHARMACOLOGIC CONSIDERATIONS

The Salicylates and the Pyrazolons—

SALICYLATES—Salicylates are endowed with an analgesic an anti inflammatory and an antipyretic action Whether the site of action may be identified in rheu matoid arthritis as the cells affected, or whether it is mediated through the central nervous system, has not been determined Surely the antipyretic action of salicylates resides in the hypothalamus and lowers the body temperature in fever through vasodilatation and dissipation of heat There may be some hemodilution and reduction in viscosity of the circulating blood Several other presumed effects of salicylates have been studied but are believed to play a minor role only in the treatment of rheumatic disorders Other actions not considered pertinent to joint disease include an increase in depth and rate of respiration, depletion of liver glycogen, increase in uric acid excretion in the urine, alteration of the acid base balance in the blood, and local gastrointestinal irritation In or near the toxic

Caronamide was the first of the group to be identified with uricosuria Probenecid is the most powerful uricosuric agent in current clinical use, also it is the least toxic of any of the substances that alter the exchange of uric acid by the kidney Probenecid finds its greatest value in the prophylaxis of chronic gouty arthritis The penicillin inhibitory action should be noted also This action is not pertinent to a discussion of rheumatic disorders Probenecid is not an anti inflammatory agent

Sulfinpyrazone—Sulfinpyrazone (Anturan), a sulfoxide analogue of phenyl butazone, is a potent uricosuric agent which has been under clinical trial for more than 2 years In short term experiments, the uricosuric and hypouricemic action is from 3 to 5 times as great as probenecid The half life of action is shorter than that of probenecid, and the drug must be administered in several divided doses each day Preliminary studies reveal that this drug is no more toxic than probenecid However extensive clinical trial is necessary before discounting the possibility of serious toxic effects upon hematopoiesis such as has been reported with the parent compound phenylbutazone

The Adrenal Steroids and ACTH—Compound E (cortisone) and adreno corticotropin (ACTH) were made available for clinical trial at approximately the same time in 1948 Attention was focused primarily upon their use in rheumatoid arthritis and acute rheumatic fever and to a lesser extent in gouty arthritis and osteoarthritis It is believed that one of the principal indications for ACTH in the arthritic field at the present time is in the treatment of the acute bout of rheumatic fever Compound E was used extensively in the management of rheumatoid arthritis, irrespective of the severity, with encouraging results originally, but has been largely replaced by more powerful anti inflammatory agents

Compound F (hydrocortisone) was the next adrenal steroid to be widely used It has replaced, in large part, Compound E In 1954, prednisone and prednisolone were found to be endowed with superior anti inflammatory properties and fewer undesirable effects upon electrolyte metabolism The next steroid that held promise was triamcinolone (Aristocort) This drug was somewhat more effective in some patients with rheumatoid arthritis but was especially so in psoriatic arthritis as well as in psoriasis uncomplicated by joint disease The untoward effects are similar to those of the other steroids save for an anabolic effect which appears as an alarming symptom in a limited few patients

The most recent steroid that has been released to the medical profession is dexamethasone (Decadron, Deronil) This has been reported to be from 6 to 8 times as potent as prednisone and 5 times as potent as triamcinolone in the treatment of rheumatoid arthritis The sodium retaining property of this compound is negligible The ulcerogenic action is similar Clinical trial with this drug has been too short to determine the side effects which develop usually upon prolonged medication [Recent reports indicate a potent and disturbing osteolytic action Ed]

There is no agreement among rheumatologists regarding indication and contraindication for the employment of the adrenal steroids in the treatment of rheumatoid arthritis I believe that their use is extremely limited in this condition A number of physicians recommend the intra articular use of Compound F following the aspiration of fluid for hydrarthrosis of a large joint A similar number recom

The development of probenecid as a uricosuric agent followed the observation by *Wolfson* and associates that caronamide inhibits the conjugation of glycine and benzoic acid and thereby alters urate exchange The conjugation involves co enzyme A and adenine triphosphate Probenecid competes effectively with ben zoate in the activation reaction but has no effect upon the subsequent transfer to glycine This interferes with the transport by forming a complex with coenzyme A that is only slightly dissociable Probenecid is endowed with no anti inflamma tory action It is rapidly and effectively absorbed from the gastrointestinal tract and is carried in the blood stream partially bound to plasma proteins The un bound portion gains access to the glomerular filtrate but is largely resorbed by renal tubules The blocking action of probenecid may be apparent within a few hours after beginning ingestion In addition to the above described findings it results eventually in a decrease in the metabolic pool and an increase in the turn over rate of uric acid It is interesting that the uricosuric action of probenecid may be nullified totally or partially by the simultaneous administration of salicylates

The incidence of toxicity is low, but there are three items that may be re counted In doses as large as 2 Gm per day there may be some gastrointestinal irritation This may be prevented by ingestion of probenecid with meals or reduc tion of the daily intake There have been a few instances reported of a skin rash In our experience, this has not been a contraindication to prolonged therapy One severe anaphylactic reaction has been reported in the literature The incidence of renal stones at one time was thought to be increased as a result of the uricosuric action of probenecid Subsequent experience has not borne out this assumption

Sulfinpyrazone (Anturan) —The pharmacologic action of this preparation is similar to probenecid Gastrointestinal distress has been observed as a side effect which appears to be common to all oral uricosuric agents The most serious prob lem however is the tendency to form uric acid gravel or uric acid stones Obviously the greater the uricosuria the greater the tendency to the formation of uric acid stones A high fluid intake is urged for all patients receiving a uricosuric drug Alkalinizing agents have been recommended on theoretical grounds to minimize this tendency In my experience the addition of alkalies has not reduced the in cidence of uric acid stones in patients with gout either on or off a uricosuric drug

The Adrenal Steroids and ACTH —A comprehensive discussion of the many pharmacologic effects of ACTH and the adrenal steroids is beyond the scope of this chapter The use of these compounds in the treatment of arthritis embraces several of the recognized actions of the steroids and probably excludes the correc tion of a deficiency of circulating hormones In other words the adrenal steroids do not replace any demonstrable hormone deficiency in any of the arthritic states under discussion

Although most of the evidence suggests that the adrenal glands appear normal histologically in patients with rheumatoid arthritis there are selected observations which suggest a functional depression of the adrenals when this malady is active The need for excessive amounts of adrenal steroids, in comparison to quantities required in recognized adrenal deficiency states implies that there may be an altered adrenal function That this may reflect a markedly increased demand by inflamed tissue for steroids or excessive catabolism is purely speculative

range, tinnitus, nausea and vomiting develop from central stimulation, followed by profound central nervous system depression Hypoprothrombinemia may lead to purpura or, in isolated instances, to severe hemorrhage

Salicylates are readily absorbed from the gastrointestinal tract and are carried in the blood bound to plasma proteins The ultrafiltrable portion readily enters the red cell as well as the joint fluid It also crosses the placental membrane A fraction of the material is conjugated with glycine to form salicyluric acid, an analogue of hippuric acid, in which compound it is excreted unchanged A small portion is converted to gentisic acid Salicyluric acid is of no value in the treatment of arthritis, and gentisic acid is of such limited value that it may be ignored in favor of salicylates if such a preparation is desired

The pharmacologic action of salicylates in acute rheumatic fever has not been clearly defined There are at least two phases in the pathogenesis in which salicylates conceivably could be operating Acute rheumatic fever usually follows a hemolytic streptococcal infection, generally in the nasopharynx The next stage is accompanied by disseminated focal inflammatory lesions, sometimes recognized as Aschoff bodies, in the cardiovascular system, in the central nervous system, in the joints, and in the serous membranes Later, substances elaborated by the strepto cocci are conjugated in the tissues to form an antigenic complex The analgesic and antipyretic action of salicylates most likely is operating in minimizing the insult of the streptococcal infection There may also be a steroidlike effect through the pituitary-adrenal axis which inhibits connective tissue changes in the several affected sites just noted Although evidence is not conclusive there are some observations which suggest that salicylates decrease hypersensitivity reactions and immunologic tissue responses

PHENYLBUTAZONE —Phenylbutazone was used originally in Europe in combi nation with aminopyrine but it soon became apparent that the pure preparation was endowed with valuable pharmacologic properties Phenylbutazone is primarily an antipyretic and analgesic preparation and has a uricosuric action similar to aminopyrine to which it is closely related and to the salicylates The first two properties are the principal reasons for recommending it in the treatment of acute gouty arthritis since any uricosuric action is unimportant in the acute phase

Colchicine —Colchicine remains an enigma in revealing its pharmacologic action It does not alter the concentration of uric acid in the serum or excretion of uric acid in the urine in gouty patients

Probenecid —The pharmacologic action of probenecid is clearly defined This drug exerts no effect upon the intermediary metabolism of uric acid nor does it alter the exchange of other electrolytes by the kidneys Probenecid causes an alter ation in the exchange of urates by the renal tubules, it decreases the reabsorption of urate in glomerular filtrate and concomitantly leads to an increased excretion of uric acid in the urine A decrease in the concentration of uric acid in the serum follows This preparation is of great value as a prophylactic agent for use in the intercritical period of gouty arthritis It does not alter the duration or severity of the acute gouty episode, nor is there any contraindication to continuing the in gestion of probenecid during the acute attack in patients who are prescribed this drug daily during the intercritical period

deficiency may lead to general muscle weakness The clinical impact of the recently available steroids upon carbohydrate metabolism is negligible The development of Cushing s syndrome is probably the most important contraindication to continued ingestion A gain in weight an increase in blood pressure a tendency to an elevated blood sugar, loss of tissue proteins, osteoporosis coronary disease, peptic ulceration, an alteration in metabolism of fat, a decrease in protein bound iodine of the blood, gonadal dysfunction, and a moon face constitute an alarming array of findings, sometimes critical but usually not so The masking of infection, such as lobar pneumonia, acute appendicitis or pulmonary tuberculosis hemorrhage from a peptic ulcer, central nervous system imbalance compression fractures of vertebral bodies and congestive heart failure are other possible serious manifestations of toxicity The corticosteroids are the usual offenders because they are the preparations customarily employed for long term maintenance If full therapeutic quantities of ACTH are administered for similar periods of time, similar toxic manifestations may develop

Gold —Gold preparations are recommended in *rheumatoid arthritis in selected* cases only They are administered by intramuscular injection in either an aqueous or an oily suspension Gold is absorbed slowly from the site of injection and is distributed in the soft tissues throughout the body As much as 80 per cent may be fixed in the tissues, with the kidney, liver, and spleen absorbing a proportionately larger share

Dangers —The toxic effects of gold may be critical, frequently they are the determining factor which interrupts a full course of treatment The incidence of severe toxic reactions has been reported to be as high as 30 per cent A few fatalities have been reported Albuminuria has been observed in a number of patients receiving gold Occasionally, hematuria or even nephrosis has developed Skin manifestations vary from a mild pruritus to severe exfoliative dermatitis Agranulocytosis thrombocytopenia, or aplastic anemia reflect an insult to the hematopoietic system Stomatitis, gastritis colitis, and possibly hepatitis reflect damage to the gastrointestinal tract Severe reactions to gold may be counteracted by the administration of dimercaprol (BAL)

A DESIGN FOR THE USE OF THE ANTIARTHRITIC DRUGS

Rheumatoid Arthritis and Osteoarthritis —

Salicylates —The salicylates are believed to be the drug of choice initially in the management of patients with rheumatoid *arthritis and osteoarthritis* The benefit is purely symptomatic and little claim has been made for any alteration basically of the articular changes which develop Symptoms may wax and wane, sometimes depending upon activity and use, at other times, without any recognized cause Either sodium salicylate or acetylsalicylic acid in amounts of 0 6 to *0 9 Gm, 3 to 5 times daily should* constitute a full therapeutic regimen This should be maintained so long as articular symptoms are severe The quantity should be reduced depending upon relief of complaints or evidence of toxicity Other measures, particularly in rheumatoid arthritis are equally valuable These include rest of acutely inflamed joints, physiotherapy, attention to nutrition and

It is presumed that adrenocorticotropic hormone promotes the elaboration of adrenal hormones, and the ultimate effect upon the target cells is similar The articular structures, the adrenal cortex, and the anterior pituitary comprise the system under consideration There are two principal groups of steroids of physiologic significance elaborated by the adrenals, i e , the mineraloids and the corticoids Each may have some overlapping effect with the other Desoxycorticosterone acetate has been used for the treatment of the electrolyte disturbance in adrenal insufficiency It has no significant clinical effect in the connective tissue diseases

PHARMACOLOGIC FEATURES —There are several pharmacologic features of the cortisones They increase gluconeogenesis at the expense of tissue proteins The inhibitory effect upon protein anabolism is brought about in the muscle by interference with carbohydrate oxidation which provides the energy for protein synthesis An exaggerated effect upon carbohydrate metabolism has led in some instances to the development of diabetes mellitus This is a reversible process and, with the newer steroids, is unimportant clinically Although Compound E helps promote fatty acid oxidation, the gluconeogenic effect is antiketogenic The uricosuric action of the steroids and ACTH is unimportant in rheumatoid arthritis as well as in gouty arthritis Steroids inhibit adrenocortical activity and thyroid function The antianabolic or catabolic function is apparent in osteoporosis delayed wound healing, and depression of formation of peritoneal adhesions The action upon the central nervous system depends upon the state of the adrenals Therapeutic quantities of Compound E have led to marked euphoria in a few patients with rheumatoid arthritis Another small number have become overt psychotics Each of the steroids employed clinically is absorbed rapidly in the gastrointestinal tract

ACTIONS IN RHEUMATISM —The mechanism of action of the steroids in rheumatoid arthritis and acute rheumatic fever is unknown The anti inflammatory effect is obvious clinically but it has not been determined whether the mechanism is one of interference with the antigen antibody mechanism, correction of an alteration of enzyme activity, interference with cellular permeability, or some other mechanism as yet unknown Steroids are not specific for any one disease or any group of disorders except for replacement of gross endocrine deficiency They depress the hypersensitivity or inflammatory processes generally Their ability to inhibit growth of pathogenic organisms or counteract bacterial toxins is nil On the contrary, any demonstrable action in infectious diseases is one of stimulating bacterial growth The response of clinical symptoms in rheumatoid arthritis is temporary, and as soon as steroids are withheld, articular symptoms return, at times in what appears to be a greater intensity In spite of presumably adequate therapeutic amounts, the pathologic changes of rheumatoid arthritis may progress unremittingly

UNTOWARD EFFECTS —The untoward effects of corticoids vary from those of minor clinical significance to sufficient severity to warrant immediate cessation of administration The sodium retaining action of Compound E may lead to fluid retention and to a gain in body weight Compound F is weaker in this property, prednisone and prednisolone are weaker still Each of the preparations promotes the excretion of potassium in the urine as sodium is retained Critical potassium

tinuing the preparation Since a gain in weight may be expected, patients shoul be placed upon a restricted caloric intake once the optimum level of body weigh is reached Large doses of the corticosteroids may lead to nitrogen depletion and negative potassium balance, hence, diets high in protein with supplementary pota. sium salt should be considered These recommendations usually are not necessar if less than 10 mg of prednisone is taken daily There appears to be no interferenc with growth and development when steroids are administered to young or adolescen children The intake of sodium chloride need not be curtailed unless there is for mation of edema Osteoporosis may be a contraindication to prolonged steroi therapy in the older individual There is no effective means known to prevent th complication Gastric irritation and the development of a peptic ulcer are sufficien to warrant the addition of antacids with each dose of steroids as well as the ad ministration of the steroids with meals The relative adrenal insufficiency may com promise the patient's ability to deal with acute stressful situations such as a sever infection a surgical procedure, or psychic trauma It may be necessary to adminis ter large amounts of adrenal steroids, 25 to 50 mg of prednisone or 100 to 200 mg of Compound F intravenously to avoid serious consequences

The intra articular administration of steroids has a limited place in the treat ment of rheumatoid arthritis, osteoarthritis, and gouty arthritis The acetate of Compound F has been used in doses ranging from 25 to 100 mg Usually, acutely affected large joints are selected but some rheumatologists have no hesitation in injecting smaller quantities in some of the smaller joints of the body such as the interphalangeals or the metacarpals Any excess synovial fluid should be aspirated before instillation of the steroid The injection may be repeated one or more times, at weekly intervals

Gold —Following salicylates and steroids in order of significance, in the treat ment of rheumatoid arthritis is gold A number of physicians who are responsible for a large group of patients afflicted with this type of joint disease recommend gold Manifestations of toxicity are the determining factor in continuing use of this preparation Physicians should be thoroughly familiar with such potentialities before prescribing a course of gold Examination of the patient at regular intervals while under treatment should be the responsibility of the physician and should not be delegated to a nurse or an assistant who may give the parenteral preparation The blood should be examined at regular intervals with particular reference to the white blood cells the red blood cells, and the concentration of platelets The urine should be studied for the presence of albumin and casts A rash may be the signal for cessation of therapy in some patients, but not in all The skin compli cations may be controlled by the adrenal steroids If toxic reactions develop to a critical degree, dimercaprol (BAL) should be administered Gold is administered in from 10 to 20 mg doses biweekly until from 200 to 300 mg have been given This constitutes one course There is no contraindication to the combined use of gold and steroids nor is there any particular advantage except as noted above

Phenylbutazone.—Phenylbutazone (Butazolidin) enjoys a limited position in the treatment of rheumatoid arthritis Not more than 200 or 300 mg should be taken daily in divided doses for continuous medication Larger quantities may be ... amounts the antiarthritic effect may be

general hygiene, prevention and correction of deformities, and physiatric measures It is believed that most rheumatologists would recommend a course of therapy embodying these general features in rheumatoid arthritis before considering other pharmacologic agents notably gold, adrenal steroids or phenylbutazone

ADRENAL STEROIDS —The adrenal steroids occupied a prominent position in the treatment of rheumatoid arthritis a few years ago Enthusiasm for their use has fluctuated, probably because the ideal steroid preparation has not yet been discovered Compound F (hydrocortisone) represented an improved product over Compound E Prednisone and prednisolone have been proved to be superior in many respects to Compound F Triamcinolone holds promise for being a yet superior product Until this hope is confirmed or dashed prednisone and prednisolone probably are the adrenal steroids of choice in the treatment of rheumatoid arthritis, if steroids are selected These may be administered orally in contrast to ACTH which must be given parenterally Steroids should be most effective in the acute inflammatory stage of the disease It is folly to expect restoration of severely distorted structural changes

Use of Adrenal Steroids If adrenal steroids are selected quantities should be kept at the irreducible minimum to achieve the submaximal antiarthritic effect rather than attempt to ameliorate the entire gamut of articular symptoms The disadvantages of such a regimen are obvious The patient becomes dependent upon large quantities of steroids and the opportunities for serious toxic effects are many It may be desirable to begin therapy with doses as large as 20 or 30 mg of prednisone but maintenance doses should be kept at levels between 5 and 15 mg and not higher The maintenance dose of dexamethasone is in the range of 2 mg a day Maintenance requirements must be judged by the clinical response rather than by any restoration of laboratory abnormalities Doses should be regulated so that the total amount recommended daily will be consumed in three or four divided amounts

Dangers The longer that patients receive adrenal steroids, the greater the likelihood that they will become addicted and the greater the problem of withdrawal Any reduction in dosage should be gradual A sudden decrease may produce alarming symptoms If the patient has been on steroids for a number of months withdrawal should be accomplished over a period of several weeks Atrophy of the adrenals following ingestion of corticoids or hypertrophy following parenteral administration of adrenocorticotropin are potential hazards in long term therapy with either preparation Although it has not been an invariable rule to alternate preparations at infrequent intervals this is desirable theoretically Since the adrenal steroids constitute the principal group of substances in this category for long term maintenance therapy, such a course should be interrupted every 3 or 4 months with a few days of adrenocorticotropin, 20 to 40 units daily I am aware of no general disadvantages to this practice and, in a minority of patients on long term steroid therapy, I recommend it

Contraindications Contraindications to steroids include a past history or symptoms suggesting current activity of a peptic ulcer, active tuberculosis, psychoneurosis severe diabetes mellitus, malignant hypertension, and generalized osteoporosis Many of the undesirable effects of steroid therapy are reversible and regress after discon

nstances in our experience, the afflicted are maintained on steroids indefinitely urely so long as acute or subacute symptoms persist

Just as in acute rheumatic fever, and without any better supporting data I ecommend a course of ACTH in full therapeutic amounts daily for 2 or 3 weeks From 40 to 80 mg ACTH gel is prescribed daily for this period of time A change s then made to prednisone usually from 15 to 30 mg daily for several weeks Thereafter the dosage is reduced gradually until a level is reached consistent with partial or complete alleviation of symptoms and avoidance of untoward or toxic ffects The use of antimalarials, sometimes recommended in the treatment of ystemic lupus will not be discussed here It is my practice to rely upon the ster oids in the treatment of these unusual connective tissue diseases

Gout and Gouty Arthritis —

Colchicine and Probenecid —Colchicine and probenecid are the two favored drugs in the treatment of gout and gouty arthritis in this clinic Colchicine has *tood the test of time as an effective arthritic agent during acute articular symp* oms Ingestion of this drug should begin at the earliest possible indication of cute symptoms A delay of even a few hours may impair the effectiveness in relief rom articular distress A good rule to follow is to recommend 1 mg of colchicine very 2 hours until from 4 to 6 such doses have been ingested or until the onset of gastrointestinal distress, i e nausea vomiting or diarrhea A gastric sedative uch as tincture of camphorated opium 5 ml, is prescribed to counteract this dis ress The dose is to be repeated every 2 hours so long as symptoms persist The dministration of colchicine intravenously in the management of the acute attack f gout may be desirable in selected instances This route should be used to com lement but not to supplement the oral use Patients with an irritable gastro ntestinal tract who tolerate oral colchicine poorly or patients undergoing surgery re candidates for this mode of administration From 3 to 5 mg may be admin tered over a period of 6 hours in divided doses (1 to 2 mg) for the full thera eutic effect In the intercritical period after the acute symptoms have been rought under control a combination of colchicine and probenecid has been roved to be highly efficacious

In patients severely afflicted with chronic tophaceous gout, from 1 to 2 Gm f probenecid and 1 mg of colchicine in divided doses are taken daily Gouty pa *ients mildly afflicted may take on an average* of 1 Gm of probenecid and 1 mg f colchicine daily Patients mildly afflicted may take minimum quantities of olchicine (0 5 mg) and probenecid (0 5 Gm) daily or at less frequent intervals Patients who suffer one or more attacks of acute gouty arthritis per year should e on colchicine and probenecid at regular intervals If these prophylactic agents re taken regularly *there need be no modification* in diet beyond the elimination f high purine substances such as liver, kidney, and sweetbreads A high fluid in ake is necessary to aid in the elimination of the additional quantity of uric acid n the urine A reasonable intake of alcoholic beverages is permitted

Phenylbutazone —Phenylbutazone has been recommended in the treatment f the attack of acute gouty arthritis *It has the advantage over colchicine* in that astrointestinal distress is avoided In doses ranging from 600 to 800 mg daily or 2 or 3 days the articular response may be similar to that of a full regimen of

inferior to that achieved by submaximal amounts of salicylates The salicylates are preferred to phenylbutazone in most instances

Acute Rheumatic Fever —

SALICYLATES —Acute rheumatic fever responds to the salicylates and to the adrenal steroids Both preparations are believed to be more specific for this malady than for rheumatoid arthritis although statistical proof in support of this assumption is lacking For several decades there was considerable difference of opinion as to whether or not salicylates were quasi specific or nonspecific in their effect upon the acute inflammatory condition Currently it is believed that salicylates are sufficiently specific that they occupy a prominent place in the treatment of this malady Subtoxic doses of salicylates should be prescribed and the daily level of intake maintained at the toleration point for a number of weeks It is suggested that 0 15 Gm of salicylate per kilogram of body weight be given This quantity should achieve a plasma level greater than 30 mg per 100 ml Although full therapeutic amounts of salicylates are effective in reducing inflammation, there is inconclusive evidence as to their value in the prevention of cardiac lesions Irre spective of this deficiency as soon as a diagnosis of acute rheumatic fever has been made or even suspected, rigorous salicylate therapy, as just described or steroid therapy, as noted below, should begin at once

CORTICOTROPIN —I prefer to use corticotropin initially in the management of acute rheumatic fever Amounts varying from 60 to 80 mg of ACTH gel are administered daily for a few days The quantity is decreased to the 20 to 30 mg range at the end of 2 weeks Thereafter a switch is made to an oral steroid prepa ration, preferably prednisone, 15 to 30 mg daily, and continued for an additional 2 or 3 weeks Maintenance doses of 5 to 10 mg of prednisone or 2 mg of dexamethasone daily are continued thereafter until all evidence of the acute process has been in abeyance for several weeks A long term follow up study will be required before evidence is produced regarding the incidence of endocardial or myocardial lesions months or years after the acute insult, as a result of salicylate or steroid medication Although the joint involvement in acute rheumatic fever does not lead to permanent damage of these structures, bed rest, adequate nutri tion, and other measures should be insisted upon for general reasons

The erythrocyte sedimentation rate is a helpful guide in determining effectiveness of therapy and activity or subsidence of the underlying process Other non specific tests such as the C reactive protein, the white blood cell count, and the elec trocardiogram may be used also as measuring sticks If cardiac failure develops, this should be treated with digitalis or other appropriate preparations, meanwhile con tinuing steroid ingestion It is particularly important under such circumstances *to restrict the salt intake, if this is ineffective, a diuretic should be administered*

Unusual Connective Tissue Disorders —

ADRENAL STEROIDS —Next in clinical significance to acute rheumatic fever, in the use of steroids, are the unusual collagen disorders, systemic lupus erythematosus, acute dermatomyositis, systemic scleroderma, and polyarteritis No one of these maladies is cured by steroids Some patients afflicted are benefited little or not at all I believe, however, that each patient suffering from one of these several morbid processes should receive a long clinical trial with steroids In most

that this (Compound E) may not be the beginning of the end (in the treatment) but only the end of the beginning" Literally, an endless number of congeners of the basic substance Compound E have been synthesized in the laboratory and tested for their anti inflammatory effect A much smaller number has been subjected to clinical trial The goal is an effective anti inflammatory agent that will reverse the disturbances of connective tissue, meanwhile remaining free of the undesirable effects which include alteration of electrolyte metabolism, formation of peptic ulcer aggravation of coronary vessel disease, central nervous system stimulation and osteoporosis The clinical use of triamcinolone has produced impressive anti inflammatory effects out of proportion to the incidence of undesirable side action At the present time, screening of steroids in this related field appears the most promising approach

The problem in acute rheumatic fever is a dual one Prevention of the immunochemical ravages of hemolytic streptococcal infections embodies the prompt and effective use of antimicrobial agents Potent antimicrobials are now available but must be employed at the earliest possible moment If these pathogens are permitted to elaborate toxins, tissue responses begin in a percentage of patients At this stage of the pathogenesis of acute rheumatic fever, salicylates and adrenal steroids appear to be effective Whether or not they are corrective in restoring the defense mechanism in the tissues and thereby preventing the development of cardiac changes has not been established This information can be collected in human beings only after a long term follow up of patients with well developed or occult acute rheumatic fever It is hoped that as more effective agents are devised for the treatment of rheumatoid arthritis these same agents will be equally effective in preventing or correcting the tissue responses in acute rheumatic fever

The specific management of the diffuse collagen disorders is less satisfactory than the management of either rheumatoid arthritis or acute rheumatic fever The problem therefore, is a more critical one The etiology and pathogenesis of each of the diffuse disorders are unknown Certain similarities suggest that an agent effective in the early stages of rheumatoid arthritis would also be of value in the early stages of the unusual disorders Hence, the development of better corticoids should make available more effective agents in the treatment of the early stages of the less common maladies The antimalarials have been employed in the treatment of systemic lupus with varying results My experience with these agents in the treatment of systemic lupus is limited In deference to my more optimistic colleagues however further study of antimalarials surely is justified It may be that outside of the malarial areas in the United States this class of drugs may have greater clinical application in the treatment of the collagen disorders than in the treatment of endemic malaria

The currently satisfactory management of patients with gout has removed some of the critical need for the development of newer and improved antigout agents Colchicine and phenylbutazone are effective in the management of the acute articular bout while probenecid is an effective uricosuric agent in the long term management in the intercritical period The advantages of a more potent uricosuric agent are limited This would consist primarily in a smaller dose per day Undoubtedly such a drug or drugs will be available in the not too distant future

colchicine If phenylbutazone is discontinued after such a period of time, the undesirable effects, agranulocytosis fluid retention, and skin rash need not be a problem I use phenylbutazone for acute gouty arthritis only if colchicine is contraindicated or if a full course of colchicine has been administered and for some reason has not produced satisfactory relief of articular symptoms Phenylbutazone is not recommended by me during the intercritical period

OTHER URICOSURIC DRUGS UNDER CLINICAL STUDY —Anturan (sulfinpyrazone) because it is a more potent uricosuric agent than probenecid has been the focus of considerable interest by rheumatologists Except for its increased potency milligram for milligram it has no recognized advantages over the more widely used and better known probenecid The potential hazard from an effect upon hematopoiesis warrants caution in the use of this drug at the present time There is yet one other uricosuric agent not mentioned previously in this chapter This is zoxazolamine (Flexin [2 amino-5 chlorobenzoxazole]) This drug was designed as a muscle relaxant and has an unanticipated action an effect upon the exchange of uric acid in the renal tubules The half life of action is less than 6 hours Its effectiveness milligram for milligram is similar to or slightly greater than that of Anturan The drug is still under clinical trial and is not recommended for use generally at this time

SALICYLATES —The anti inflammatory property of the salicylates in the management of acute gout is less satisfactory than that of colchicine Since they negate the uricosuric action of probenecid they have no role to play as a prophylactic agent if probenecid is prescribed regularly There has been a renewal of interest in the use of large amounts of salicylates daily as prophylaxis However I believe that colchicine and probenecid should be the foundation stones in the treatment of gouty arthritis

RATIONAL BASIS FOR NEW DRUGS FOR THE RHEUMATIC DISEASES

It is believed that any therapeutic agent of value in osteoarthritis must be applied as a preventive agent rather than a corrective one Since osteoarthritis is considered to be one manifestation of the aging process that appears prematurely in some individuals preventive therapy must begin in the early decades of life The precise mode of action of the preventive agent would be purely speculative Because cartilage bone and synovial tissue participate in the production of osteoarthritis maintenance of normal structure of soft tissues as well as bony tissues would be sought Possibly a deficiency of enzymes or adrenal steroids might be responsible Any approach to the problem seems rather fruitless at the present time and basic investigations must be pursued before any rational approach to the development of therapeutic agents would be justified

Considerably more progress has been made in our understanding of the pathogenesis and treatment of rheumatoid arthritis even though clinical results continue to be discouraging in a number of patients The status as expressed by Hench when Compound E was first made available in 1948 is still valid He paraphrased Winston Churchill's famous quotation and stated We certainly realize ourselves

that this (Compound E) may not be the beginning of the end (in the treatment) but only the end of the beginning" Literally, an endless number of congeners of the basic substance Compound E have been synthesized in the laboratory and tested for their anti inflammatory effect A much smaller number has been subjected to clinical trial The goal is an effective anti inflammatory agent that will reverse the disturbances of connective tissue, meanwhile remaining free of the undesirable effects which include *alteration of electrolyte metabolism, formation* of peptic ulcer, aggravation of coronary vessel disease, central nervous system stimulation and osteoporosis The clinical use of triamcinolone has produced impressive anti inflammatory effects out of proportion to the incidence of undesirable side action At the present time, screening of steroids in this related field appears the most promising approach

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but will require long-term clinical trial before the physician is assured that the drug is endowed with as low an incidence of toxicity as is probenecid

It is important in the prophylactic management during the intercritical period for patients with gout to achieve maximum uricosuria A decrease in the metabolic pool and a decrease in the concentration of uric acid in the serum should lead eventually to withdrawal of the urate deposits in bone and soft tissues Such a state would represent a normal situation and the patient would theoretically be immune to acute attacks of gout Yet another approach to the problem would be the correction of the underlying pathogenic mechanism If this is a disturbance of the intermediary metabolism of uric acid, an inhibitor of xanthine oxidase might be effective Such a preparation was available for clinical trial a few years ago and found to be ineffective in so far as could be determined in altering the concentration of uric acid in the serum or the excretion of this substance in the urine

SELECTED REFERENCES

Bishop, C, Rand, R, and Talbott, J H The Effect of Benemid (p-[di n propylsulfamyl] benzoic acid) on Uric Acid Metabolism in One Normal and One Gouty Subject, J Clin Invest 30 889, 1951

Bishop C, and Talbott, J H Uric Acid Its Role in Biological Processes and the Influence Upon It of Physiological, Pathological and Pharmacological Agents, Pharmacol Rev 5 231, 1953

Committee of the American Rheumatism Association Primer on the Rheumatic Diseases, J A M A 152 323 405 552, 1953

Engleman, E P, Krupp M A, Forsham, P Griffin A C, Johnson H, Green, T, and Goldfen, A Studies on the Effect of Phenylbutazone in the Treatment of Gout Am J Med 15 414, 1953

Fischel, E E, Frank, C W, and Ragan C Observations on Treatment of Rheumatic Fever With Salicylate, ACTH and Cortisone Appraisal of Signs of Systemic and Local Inflammatory Reaction During Treatment the Rebound Period and Chronic Ac

Fr nt of the Patient With Rheumatoid Ar
1953

G of Management of Gout, Am J Med
13 744, 1952

1949

Hollander, J L Intra articular Hydrocortisone in the Treatment of Arthritis, Ann Int Med 39 735, 1953

Kersley, Function in Rheu

Lowman, With Rheumatoid

Lukens, F ston Co

Marson, Value of Sodium Salicylate in Treatment, Quart J Med 22 331, 1953

Smith, G E, and Wilson, G M Treatment of Gout, A M A Arch Int Med 97 783, 1956

Talbott, J

Talbott,

Wolfson

Yü T F, Burns, J J, and Gutman, Alexander, B Results of a Clinical Trial of G 28315, a Sulfoxide Analog of Phenylbutazone, as a Uricosuric Agent in Gouty Subjects, Arth & Rheum 1 532, 1958

Chapter 33

THE CHOICE OF DRUGS FOR CANCER AND ALLIED DISEASES*

David A. Karnofsky, M.D.

INTRODUCTION

In the past twenty years, and particularly since *1946,* there has been an extraordinary search in progress for drugs effective in controlling the growth or accomplishing the destruction of neoplastic cells wherever they occur in the body. The list of substances that have been proposed for clinical use is long and it is increasing in length. It is difficult and time consuming to establish the therapeutic efficacy of a palliative drug in cancer, and new drugs are being introduced for general clinical use before a scientific amenity—clear proof of distinctive or unique activity—has been observed. Thus, the real progress that has been made in chemotherapy of cancer is sometimes overshadowed, confused, or distorted by immoderate or premature claims or actual misrepresentations of the benefits achieved by new forms of treatment. A proper therapeutic appraisal of the value of the available drugs must be based on convincing clinical evidence. An acceptable chemotherapeutic agent should have definite and specific indications and should not be employed merely as part of a general barrage against the many presently insoluble therapeutic problems in patients with disseminated or advanced neoplastic disease.

GENERAL CONSIDERATIONS

There are no drugs effective against *all forms or all stages of cancer.* Several basic considerations are important in determining the indications for a chemotherapeutic agent and in selecting the proper drug for a specific type of cancer and at a particular stage of the disease.

Many different types of cancer occur; these vary as to site of origin, histologic appearance, retention of functional properties from their tissue of origin, rate of growth, and pattern of metastases. Even in patients with the same type of cancer, the disease, in each individual, runs a distinctive course. Also, a specific form of cancer may show a wide range of responsiveness to established chemo

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SELECTED REFERENCES

Bishop, C, Rand, R, and Talbott, J H The Effect of Benemid (p [di n propylsulfamyl] ... abolism in One Normal and One Gouty Subject, J

... Its Role in Biological Processes and the Influence ... ological and Pharmacological Agents, Pharmacol

Committee of the American Rheumatism Association Primer on the Rheumatic Diseases, J A M A 152 323, 405 552, 1953

Engleman, E P, Krupp, M A Forsham P, Griffin, A C, Johnson H, Green T and Goldfen, A Studies on the Effect of Phenylbutazone in the Treatment of Gout Am J Med 15 414, 1953

Fischel, E E, Frank, C W, and Ragan C Observations on Treatment of Rheumatic Fever With Salicylate, ACTH and Cortisone Appraisal of Signs of Systemic and Local Inflammatory Reaction During Treatment, the Rebound Period and Chronic Activity, Medicine 31 331, 1952

Freyberg, R H, and Stevenson, C R Management of the Patient With Rheumatoid Arthritis, M Clin North America 37 1235, 1953

Gutman, A B, and Yu, T F Current Principles of Management of Gout, Am J Med 13 744, 1952

Hart ...

Hen ... 1949

Hollander, J L Intra articular Hydrocortisone in the Treatment of Arthritis, Ann Int Med 39 735, 1953

Kersley, G D ... and Liver Function in Rheu ...

Lowman, ... the Patient With Rheumatoid ...

Lukens, F ... The Blakiston Co

Marson, ... nce to the Value of Sodium ...

Smith, G ... A Arch Int Med 97 783 1956

Talbott, J H, Bishop, C, Norcross B M and Lockie, L M The Clinical and Metabolic ... n Physicians 64 372, 1951

Talbott, J ... Grune & Stratton, Inc

Wolfson ... Transport and Excretion of Uric ... Effect of Caronamide (Abst), ...

Yu, T F, Burns, J J, and Gutman, Alexander, B Results of a Clinical Trial of G 28315, a Sulfoxide Analog of Phenylbutazone, as a Uricosuric Agent in Gouty Subjects Arth & Rheum 1 532, 1958

patient is acutely ill with fever, bleeding manifestations, infection, or rapid progression of the disease

A folic acid antagonist may be started as soon as the diagnosis is established if the patient is in good condition it is given alone Treatment may have to be continued for 4 to 6 weeks with an antifolic in order to produce a satisfactory hematologic response, in patients in poor condition it is safer to try to alleviate the acute problem with the adrenal steroids while the trial of a folic acid antagonist is started The folic acid antagonists induce complete hematologic remissions in about 35 per cent of children, and in another 15 to 20 per cent the clinical situation is markedly improved, although the blood picture is not entirely restored to normal Remissions may continue for 3 to 6 months or longer, when the patient relapses he *may respond again to a course of folic acid antagonist therapy if a satisfactory* response has occurred

The purine analogue mercaptopurine (Purinethol) may be used initially in the same manner as the folic acid antagonists, as well as in patients who have become resistant to the folic acid antagonists Mercaptopurine produces hematologic remissions in 50 to 70 per cent of leukemic children, which usually last for an average of 3 to 4 months, but once resistance appears the patient does not ordinarily respond to a second course of treatment The glutamine antagonist, azaserine (seryl), while it does not exert a primary effect on the disease, may enhance the action of mercaptopurine to produce more prolonged, and a higher percentage of, complete hematologic remissions

Using the folic acid antagonists and mercaptopurine, with or without azaserine, to induce sustained remissions, with short courses of the adrenal steroids for acute situations, about 70 per cent of leukemic children can be maintained in good general health during the major portion of their illness Survival has been prolonged in 50 per cent of the children to 1 year or longer as compared to an average survival time of 4 months prior to the time when these agents became available During the final relapse the child is refractory to all known forms of treatment and death usually occurs from infection or bleeding

Drugs of Choice —

Adrenal Steroids —Prednisone is the adrenal steroid of choice Treatment is usually begun with large doses—25 to 50 mg daily divided into 4 to 6 doses daily Within 1 to 2 weeks, if a favorable response is evident from the patient's *clinical condition* and his peripheral blood and bone marrow pictures, the dose may be decreased, and, finally, discontinued in 7 to 10 days Large doses are given initially because a child unresponsive to a lower dose, may go into a prompt hematologic remission at a higher one Nevertheless, if the leukocyte count is markedly elevated, or the child has bulky lymph nodes and a greatly enlarged liver and spleen these large doses must be given cautiously, since in responsive cases rapid dissolution of the neoplastic cells may result in severe hyperuricemia and renal injury The leukocyte count and renal function should be followed carefully, and the prednisone dosage temporarily interrupted when a rapid fall in the leukocyte count occurs In patients in the resistant terminal stage, doses of 100 mg of prednisone may be given with partial alleviation of fever and bleeding tendencies, although a hematologic remission is no longer expected

therapeutic agents, suggesting numerous differences in the metabolism of the cancer cells or the host. In this complicated situation, established drugs are not uniformly or predictably effective despite careful case selection under well defined conditions. A useful drug, however, should exhibit a consistent range of therapeutic activity in specific situations, with improvement lasting for an appreciable period of time.

Since the available drugs are feeble as therapeutic agents in most cases, there are honest differences of opinion as to when a drug should be given and for what purpose. Some prefer treating patients with disseminated cancer early, in the hope of delaying the disease, whereas others wait to start chemotherapy until the patient has symptoms and measurably progressive disease. Late in the disease, some physicians pursue an aggressive therapeutic policy, even when there is little hope of obtaining a satisfactory response, whereas others decry these efforts as improper. One looks forward to the day when these differing views are rendered irrelevant by more effective agents. Nevertheless, we believe that the patient with advanced cancer deserves active treatment, and the honest physician who attempts thus to provide solace to the patient and family in desperate situations exemplifies the highest purposes of medicine.

The chemotherapeutic agents in cancer are given in many instances, to the maximum tolerated dose in an attempt to elicit a therapeutic response. Severe and sometimes prolonged host toxicity may occur with some drugs, and their pharmacology must be clearly understood for their safe and yet adequate administration.

While this report is concerned with drugs, it must not be forgotten that x-ray therapy is the single most important method available for the palliation of advanced cancer, and it must be considered also in most situations where the use of chemotherapeutic agents is entertained. In many instances local irradiation will prove to be the treatment of choice and in other cases it will be given in association with chemotherapy.

With these general comments, we can turn to the specific drugs useful in each type of cancer. A few of the appropriate features of each form of neoplastic disease as it relates to chemotherapy will be reviewed, and then the drugs of choice will be presented in detail.

CLINICAL CONSIDERATIONS

Acute Leukemia

Acute leukemia in children, young adults, and adults has different ranges of responsiveness to the available chemotherapeutic agents, and different sequences of drug administration are indicated. Each age group will be discussed.

Children.—The folic acid antagonists, the purine analogues, and the adrenal steroids are effective in producing temporary remissions of the disease. When the leukemic process becomes resistant to one drug, and relapse occurs despite continuing therapy, it may still respond to another type of antileukemia therapy. Adrenal steroids are promptly effective in about 70 per cent of the patients, but remissions are usually brief, and even if the treatment is maintained, relapse often occurs within 2 to 4 weeks. Adrenal steroids are thus used for a brief period when the

patient is acutely ill with fever, bleeding manifestations, infection, or rapid progression of the disease

A folic acid antagonist may be started as soon as the diagnosis is established, if the patient is in good condition it is given alone Treatment may have to be continued for 4 to 6 weeks with an antifolic in order to produce a satisfactory hematologic response, in patients in poor condition it is safer to try to alleviate the acute problem with the adrenal steroids while the trial of a folic acid antagonist is started The folic acid antagonists induce complete hematologic remissions in about 35 per cent of children, and in another 15 to 20 per cent the clinical situation is markedly improved, although the blood picture is not entirely restored to normal Remissions may continue for 3 to 6 months or longer, when the patient relapses he may respond again to a course of folic acid antagonist therapy if a satisfactory response has occurred

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Despite persistent adrenal steroid therapy, resistance ultimately develops Sustained treatment with the adrenal steroids usually produces only brief remissions, and children treated with hormones alone have shown no important prolongation of survival time For this reason, prednisone is usually reserved for acute clinical situations

The consequences of large doses of the adrenal cortical hormones are well known Children develop moon facies, a voracious appetite and obesity, and hypertension with occasional coma Fluid retention has not been an important problem with prednisone, and it is of interest that steroid induced diabetes mellitus is rarely seen in children With short treatment periods these complications need not be severe, they occur in the late stages of the disease when prolonged adrenal steroid therapy at very high doses is used in the hope of prolonging life While adrenal steroids increase susceptibility to infection, when the leukemic patient is in relapse and infection is present, dosage is usually increased because of the stressful situation and in the hope of improving hematopoiesis Generally supplemental potassium or testosterone has not been necessary with prednisone therapy

The mechanism of action of the adrenal steroids on leukemic cells, or the nature of cellular resistance has not been determined Adrenal steroids are lympholytic and cells of acute leukemia may possibly retain some of the responsiveness of normal lymphocytes These hormones inhibit the growth of some mesenchymal cells, and the leukemic cells may be biochemically related to these In responsive cases the action of the adrenal steroids on the leukemic marrow is very specific The abnormal cells disappear promptly, thereby decompressing the marrow and permitting, even in the presence of the hormone, the rapid regeneration of normal bone marrow elements By contrast, the antimetabolites, in therapeutic doses ordinarily cause depletion of all elements of the leukemic marrow following which the normal hematopoietic elements gradually reappear to produce a hematologic remission Thus, the antimetabolites are bone marrow depressants in the range of the therapeutic dose whereas the adrenal steroids do not depress the normal bone marrow In further contrast the polyfunctional alkylating agents and x rays which destroy lymphocytes and leukemic cells and depress the normal bone marrow, do not produce hematologic remissions in acute leukemia

Related Adrenal Steroids of Clinical Value There is no evidence for any qualitative differences in the therapeutic activity of prednisone and other adrenal steroids or ACTH in acute leukemia

Cortisone was initially used in the treatment of leukemia, at doses of 100 to 150 mg in divided doses daily Because of the frequent tendency to salt and fluid retention it has been largely supplanted by prednisone Hydrocortisone is the intravenous preparation of choice In patients unable to take the adrenal steroids by mouth, or in whom rapid treatment is essential, hydrocortisone succinate (Solu Cortef), 100 to 200 mg, may be given daily by direct injection as an infusion by dissolving it in 5 per cent glucose in water

Triamcinolone has no apparent advantage over prednisone in acute leukemia

There is rarely any indication for the use of ACTH However in patients who are bleeding severely prompt improvement has been obtained by the continuous infusion of ACTH This is presumably due to its rapid action in stimu

lating high levels of adrenal steroid production by the adrenal, rather than to the production of adrenal steroids with high antileukemic activity In children, 25 mg of ACTH has been dissolved in 5 per cent glucose and given by continuous infusion over a 24 hour period Intramuscular injections are avoided in acute leukemia in relapse because of the severe bleeding tendency

FOLIC ACID ANTAGONISTS —Amethopterin (Methotrexate) is the folic acid antagonist of choice The usual daily dose in children is 2 5 mg In most instances this dose is given daily for 7 to 10 days, if there is no evidence of fall in leukocyte count or oral toxicity the dose may be increased to 3 75 mg for another week or 10 days and then in the absence of toxicity, to 5 mg per day Ordinarily, within 2 to 3 weeks amethopterin will produce changes in the peripheral blood picture and bone marrow with definite evidence of oral toxicity If renal function is impaired the toxicity of amethopterin may be markedly enhanced due to its delayed excretion, and a lower initial dose is given

It is essential in acute leukemias to give an adequate trial of amethopterin It may be necessary to produce toxic manifestations on several separate occasions or to maintain the patient on the edge of toxicity for several weeks before a satisfactory hematologic remission occurs When a complete hematologic remission occurs as determined by examination of the bone marrow and the absence of clinical signs of the disease, amethopterin therapy is usually discontinued until signs of relapse appear Early relapse is usually detected first in the bone marrow, and frequent bone marrow aspirations are therefore essential for proper management When relapse begins amethopterin is restarted, and second and third remissions in the responsive cases are frequent occurrences

If a complete hematologic remission does not occur, amethopterin may be continued at near toxic levels as long as the patient remains in satisfactory clinical condition Clinical improvement in some cases may be maintained for months on amethopterin without a complete bone marrow remission If the patient's condition continues to deteriorate after an adequate trial of amethopterin, resistance is clearly present and the drug is discontinued Some clinics have continued amethopterin at maintenance dosage during periods of remission, but our preference has been intermittent therapy In patients with leukemic involvement of the meninges which is not responding well to systemic therapy, amethopterin has been given intrathecally The usual dose is 0 3 to 0 5 mg per kilogram of body weight, and, because of its slow absorption from the spinal fluid, it may produce severe systemic toxicity

Appreciation of the toxic manifestations of amethopterin is essential to adequate therapy, since toxicity is frequently induced in order to obtain a good response There are no immediate reactions to the ingestion of amethopterin The earliest and most easily recognized signs of toxicity are oral ulcerations These may occur on the lips the buccal mucosa, tongue, or palate These lesions may be confused with herpes simplex or the oral complications of leukemia If amethopterin is continued, these ulcerations usually progress and diarrhea may then appear, due to ulcerations of the lower digestive tract This may be very severe, and intestinal hemorrhage, particularly in leukemic patients, is a formidable possibility

Despite persistent adrenal steroid therapy, resistance ultimately develops Sustained treatment with the adrenal steroids usually produces only brief remissions, and children treated with hormones alone have shown no important prolongation of survival time For this reason, prednisone is usually reserved for acute clinical situations

The consequences of large doses of the adrenal cortical hormones are well known Children develop moon facies, a voracious appetite and obesity, and hypertension with occasional coma Fluid retention has not been an important problem with prednisone, and it is of interest that steroid induced diabetes mellitus is rarely seen in children With short treatment periods these complications need not be severe, they occur in the late stages of the disease when prolonged adrenal steroid therapy at very high doses is used in the hope of prolonging life While adrenal steroids increase susceptibility to infection, when the leukemic patient is in relapse and infection is present, dosage is usually increased because of the stressful situation and in the hope of improving hematopoiesis Generally, supplemental potassium or testosterone has not been necessary with prednisone therapy

The mechanism of action of the adrenal steroids on leukemic cells, or the nature of cellular resistance has not been determined Adrenal steroids are lympholytic, and cells of acute leukemia may possibly retain some of the responsiveness of normal lymphocytes These hormones inhibit the growth of some mesenchymal cells, and the leukemic cells may be biochemically related to these In responsive cases the action of the adrenal steroids on the leukemic marrow is very specific The abnormal cells disappear promptly, thereby decompressing the marrow and permitting even in the presence of the hormone, the rapid regeneration of normal bone marrow elements By contrast, the antimetabolites, in therapeutic doses, ordinarily cause depletion of all elements of the leukemic marrow following which the normal hematopoietic elements gradually reappear to produce a hematologic remission Thus, the antimetabolites are bone marrow depressants in the range of the therapeutic dose whereas the adrenal steroids do not depress the normal bone marrow In further contrast the polyfunctional alkylating agents and x rays which destroy lymphocytes and leukemic cells and depress the normal bone marrow, do not produce hematologic remissions in acute leukemia

Related Adrenal Steroids of Clinical Value There is no evidence for any qualitative differences in the therapeutic activity of prednisone and other adrenal steroids or ACTH in acute leukemia

Cortisone was initially used in the treatment of leukemia at doses of 100 to 150 mg in divided doses daily Because of the frequent tendency to salt and fluid retention it has been largely supplanted by prednisone Hydrocortisone is the intravenous preparation of choice In patients unable to take the adrenal steroids by mouth, or in whom rapid treatment is essential, hydrocortisone succinate (Solu Cortef) 100 to 200 mg, may be given daily by direct injection as an infusion by dissolving it in 5 per cent glucose in water

Triamcinolone has no apparent advantage over prednisone in acute leukemia

There is rarely any indication for the use of ACTH However in patients who are bleeding severely prompt improvement has been obtained by the continuous infusion of ACTH This is presumably due to its rapid action in stimu

Other drugs with antifolic activity have been tried clinically Two major types are the diaminodichlorophenyl pyrimidines, which are related to the antimalarial drug, pyrimethamine (Daraprim), and the dihydrotriazines While these drugs may have some intrinsic therapeutic effect on acute leukemia they are not effective in amethopterin resistant patients, and they are more difficult to use

PURINE ANALOGUES —Mercaptopurine (Purinethol) is the purine analogue of choice The usual daily dose is 2 5 mg per kilogram of body weight (a dose of 25 to 75 mg per day) It may be taken as a single dose at any time during the day There are no immediate toxic manifestations, but, after prolonged use, nausea or abdominal discomfort may develop These may be corrected by lowering the dose or using another purine analogue

The initial dose of 2 5 mg per kilogram is well tolerated and can usually be continued for long periods Hematologic remissions may occur without any important symptoms of host toxicity As with amethopterin, adequate dosage is essential This often requires the production of severe leukopenia and bone marrow hypoplasia due to the elimination of the leukemic elements, then normal hematopoiesis may begin while Purinethol is continued In some cases, however, persistent leukopenia and bone marrow aplasia may be due to the toxic action of the drug, and brief interruption in treatment will permit the recovery of the normal constituents of the bone marrow Resistance develops fairly rapidly to Purinethol and if treatment is interrupted relapse is fairly prompt Purinethol is given, therefore at maintenance doses, usually at the level of 1 5 to 2 5 mg per kilogram daily, and the drug is discontinued when definite hematological signs of relapse occur Increasing the dose has rarely been useful The average remissions on Purinethol last 3 to 4 months

The principal toxicity produced by Purinethol is a decrease in the formed elements of the blood and aplasia of the bone marrow This occurs regularly at excessive doses and can lead to death During treatment the peripheral blood picture should be examined at frequent intervals and the dose diminished if an unexpected fall in the leukocyte or platelet counts occurs Bone marrow recovery after discontinuation of Purinethol is usually prompt Occasional patients develop skin eruptions, apparently a sensitivity reaction, Purinethol has been observed to be pyrogenic in rare instances

Purinethol is adequately absorbed by mouth and is excreted in the urine in part as mercaptopurine and 6 thiouric acid It presumably acts by interfering with the incorporation of purines into nucleic acid thus inhibiting cellular proliferation While the leukemic process develops a fairly prompt and marked resistance to Purinethol, these resistant cells may still be responsive to amethopterin

Related Compounds 6 Thioguanine, 6 chloropurine, and 6 methylmercaptopurine are probably as effective as mercaptopurine in acute leukemia The dose of 6 thioguanine and 6 methylmercaptopurine (2 5 mg per kilogram of body weight per day) is the same as mercaptopurine, whereas the 6 chloropurine dose is about 10 times more (20 to 30 mg per kilogram each day)

These drugs are tolerated as well as Purinethol and occasionally a patient who is nauseated on Purinethol will take one of the other purine analogues without difficulty Occasional patients on 6 chloropurine have developed evidence of liver

Another major action of amethopterin is bone marrow depression, and even in normal individuals it can cause fatal aplasia This is usually seen in the peripheral blood as a decrease in granulocytes, followed by thrombocytopenia and reticulocytopenia and bleeding manifestations Anemia results from bleeding and interruption in red cell formation The bone marrow is hypoplastic but contains megaloblasts If the drug is discontinued and the patient sustained with blood transfusions bone marrow recovery may begin in 5 to 7 days In favorable situations amethopterin may selectively destroy the leukemic cells with relatively little injury to normal hematopoiesis Nevertheless it may be necessary to produce definite marrow hypoplasia by persistent therapy, and the normal blood forming elements will then regenerate preferentially In patients with elevated leukocyte counts, amethopterin may cause a rapid fall of the white cell count to low levels, in these situations the drug should be started cautiously

Other less frequent undesirable effects of amethopterin consist of increased pigmentation alopecia and diminished resistance to infection In children on prolonged amethopterin therapy cirrhotic changes in the liver have been observed, apparently related to a chronic nutritional deficiency state

The toxic and therapeutic effects of amethopterin may be prevented by the simultaneous administration of the citrovorum factor (Leucovorin), a tetrahydro formyl derivative of folic acid Folic acid is without protective value against amethopterin Once overt toxic effects have appeared they cannot be corrected by Leucovorin

Amethopterin interferes with the functions of folic acid a vitamin which is essential for the proliferation of many normal tissues including the blood forming organs and the lining of the intestinal tract Amethopterin prevents the conversion of folic acid to citrovorum factor and also interferes directly with its action The citrovorum factor is necessary for the transfer of single carbon fragments in the de novo synthesis of purines purines are essential components of nucleic acid which are replicated during cellular proliferation and of coenzymes vital to the energetics of the cell It is presumably the block in purine synthesis which prevents the formation of leukemic cells Ultimately the leukemic process becomes resistant to these agents this is attributed to the appearance of mutant leukemic cells with altered metabolic pathways

Related Compounds A host of other 4 amino analogues of folic acid have been used clinically in the hope of finding one more effective against leukemia

Aminopterin was the first 4 amino analogue of folic acid to be used clinically It is approximately 5 times as active by weight as amethopterin and the usual daily dose in children is therefore 0 25 to 0 5 mg by mouth While Aminopterin is as effective as amethopterin in our experience amethopterin is more convenient to use Other changes in the 4 amino folic acid molecule have produced less toxic derivatives but this has not enhanced the therapeutic ratio of the drug and there is no evidence for the existence of a more specific antileukemic analogue of folic acid Furthermore cross resistance develops to these analogues so a leukemia patient resistant to amethopterin is also resistant to Aminopterin

Aminopterin is water soluble and can be given intramuscularly or intravenously, although there is rarely any indication for its parenteral use

mercaptopurine is the drug of choice About 30 per cent of the patients who survive longer than 3 weeks *after the beginning* of mercaptopurine therapy will obtain hematologic and clinical improvement which usually lasts *for 2 to 4 months* and *sometimes longer* This agent should be started as soon as posible, at a *dose of 2 5* mg per kilogram of body weight per day, and continued as long as there is any evidence of improvement or sustained clinical remission

Ordinarily less than 5 per cent of young adults treated with amethopterin *develop* hematologic improvement However, patients who have *responded to* mercaptopurine and then become resistant may occasionally show striking hematologic and clinical remissions on amethopterin This suggests that in some cases *mercaptopurine resistant cells have acquired an increased sensitivity to amethopterin* A vigorous trial of amethopterin is indicated in these situations using an initial dose of 5 0 mg per day and raising or lowering the dose on the basis of the hematologic findings and evidence of oral toxicity

Older Adults—Over the age of 40 there is a marked decrease in the response *of leukemic patients to the drugs effective* in *childhood leukemia Prednisone* rarely produces any improvement in hematopoiesis, although in acute situations doses of 100 mg per day *may diminish fever and bleeding manifestations In* our experience a dose of 100 mg per day for 2 to 3 weeks is an adequate trial since larger doses, up to 1,000 mg per day, have not produced additional benefit The large doses of prednisone used in these patients may produce hyperglycemia and occasionally diabetic coma and fluid retention

The drug of choice is mercaptopurine, which induces hematologic remission in about 20 to 30 per cent of patients for 2 to 4 months or longer The usual dose is 2 5 mg per kilogra [illegible] some-
times to the point of [illegible]
of producing maxim[illegible]
regeneration of normal bone marrow 6 *Chloropurine, which was investigated after* mercaptopurine, appeared to give a slightly higher remission rate This was apparently due to the more aggressive use of 6 chloropurine, because later, when mercaptopurine was given to produce equivalent degrees of marrow depression, the response rate from the two drugs was similar While amethopterin alone does not have any important therapeutic activity in *adult leukemia, it has* induced an appreciable number of partial and complete remissions in patients who responded and then developed resistance to mercaptopurine

Miscellaneous Compounds—The polyfunctional alkylating agents, colchicine, urethan and Fowler's solution have no consistent therapeutic action on acute leukemia

Chronic Myelocytic Leukemia

This disease runs a much more prolonged course than acute leukemia, and there is little evidence that life is conspicuously prolonged by treatment The average *survival time is 3 to* 4 years from clinical onset, and by proper treatment the patient may be maintained in relatively good health during the major portion of the course of the disease During the early stages of chronic myelocytic leukemia patients are extremely responsive to many different *forms of treatment*, and the treat

damage While this may be coincidental and attributable to a serum hepatitis from the numerous blood transfusions these patients receive, the possible hepato toxic effect of 6 chloropurine should be kept in mind Leukemic cells in mice and man have developed cross resistance to these agents, indicating the similarity in their mechanism of action A number of other purine analogues have been examined clinically thus far, including 8 azaguanine, 2,6 diaminopurine, 6 methylpurine, purine and aminonucleoside, without consistent evidence of therapeutic activity in acute leukemia

Glutamine Antagonists —The drug of choice in acute leukemia is azaserine (serynl), 25 mg A dose of 10 mg per kilogram may be tolerated for several days, but when combined with mercaptopurine the toxicity of azaserine is enhanced When used in combination therapy, mercaptopurine is given at the usual dose of 2 5 mg per kilogram, and azaserine at 1 25 to 2 5 mg per kilogram

When given alone, azaserine has had little effect on acute leukemia, it is being used in combination with mercaptopurine since the combination appears to pro long the hematologic remissions produced by mercaptopurine When resistance develops to mercaptopurine, however, the addition of azaserine is of negligible value

The principal toxic effect of azaserine is the development of a red and sore tongue and in some cases, oral ulcers Continuous treatment may also cause diarrhea, in a few cases the leukocyte and platelet counts are reduced All manifesta tions of toxicity subside within 3 to 5 days after the drug is stopped

Azaserine is a potent inhibitor of purine synthesis, presumably by interfering with the incorporation of nitrogen into the 3 position of the purine skeleton a step dependent on the presence of glutamine While it inhibits tumor growth in laboratory animals, and interferes with purine synthesis in vivo and in vitro azaserine has had minimal effects on the proliferation of leukemic cells

Related Compounds 6 Diazo 5 oxo l norleucine (DON) is closely related to azaserine structurally and is 40 to 50 times as active by weight It has shown no remarkable activity in acute leukemia and comparative studies on the combination of azaserine mercaptopurine and DON mercaptopurine are incomplete The usual dose of DON is 0 1 to 0 2 mg per kilogram (5 to 10 mg) daily by mouth Its toxic manifestations are similar to azaserine, but mercaptopurine does not seem to aggravate the oral toxicity caused by DON thus DON can be used in nearly full doses in combination with mercaptopurine

Young Adults —The treatment of acute leukemia in young adults is similar to that in children, but the available drugs are less consistently effective In acute problems, prednisone is the drug of choice The initial dose is 100 mg daily by mouth, usually in divided doses (4 to 6 times daily), and this dose is decreased as soon as signs of a hematologic response appear The hematologic response in young adults is usually slower than in children, and 3 to 4 weeks of treatment may be necessary before maximum improvement occurs In some cases a smaller dose is effective for maintenance purposes and the patient is continued on this for several weeks while antimetabolite therapy is established Prednisone will produce some evidence of improvement in about 50 per cent of the patients

In patients responding to prednisone, or initially in patients in good condition,

BUSULFAN—Busulfan (Myleran) is the drug of choice in chronic myelocytic leukemia The usual dose is 6 to 10 mg per day, and at the beginning the patient is followed at weekly intervals The dose may be raised or lowered, depending on the white cell count, until a gradual but adequate response has been obtained In early cases it is often worth while to stop Myleran to determine the length of the remission without treatment Prolonged remissions would lead to intermittent courses of busulfan, brief remissions would indicate maintenance therapy In chronic myelocytic leukemia the leukocyte count is a good guide to treatment since in contrast to other conditions, the leukocyte count stops falling within a few days after treatment is stopped

In responsive patients busulfan can maintain the patient in good clinical remission for 2 years or longer As the disease progresses, however, it becomes more resistant to treatment, and the leukocyte count may rise and the spleen continue to enlarge despite increasing doses of busulfan It then becomes apparent that normal hematopoiesis is being suppressed by doses that are no longer controlling the disease In other instances, the patient abruptly goes into an acute blastic phase, and busulfan should be discontinued

TEM—Other polyfunctional alkylating agents may be used in place of busulfan TEM (triethylene melamine) may be given orally or intravenously The dose ranges from 2 5 to 5 mg, and it is taken with plain water before breakfast on an empty stomach Some clinics administer each dose with 2 Gm of sodium bicarbonate to prevent the inactivation of TEM by the gastric acidity, I do not believe this practice is essential About 50 per cent of patients tolerate this dose without difficulty, whereas the remainder may develop a brief period of nausea and occasional vomiting The initial dose is 2 5 mg daily for 4 days, and then further dosage is determined on the basis of weekly blood counts If there is a prompt fall in the leukocyte count, treatment is interrupted, but if it remains high, doses of 5 mg weekly may be necessary While the therapeutic effects of TEM parallel those of Myleran, the latter is easier to use and better tolerated

The routine intravenous dose of TEM is 0 04 mg per kilogram (2 to 3 mg) for 3 to 4 days It is available in vials containing 5 mg, the drug is dissolved in saline, and the appropriate dose then is injected into the tubing of a running intravenous infusion of physiologic saline Intravenous TEM is the drug of choice when it is desirable to produce a prompt fall in the leukocyte count It should be noted again, however, that the rapid dissolution of leukemic cells may cause hyperuricemia and renal injury

Nitrogen mustard (HN_2, Mustargen), Thio TEPA (triethylene thiophosphoramide, TSPA) and a number of other related compounds have been used, but they offer no advantages over busulfan or TEM in chronic myelocytic leukemia

Purine Analogues—The agent of choice is mercaptopurine (Purinethol) At an initial dose of 2 5 mg per kilogram by mouth this drug produces excellent control of the disease in responsive patients Maintenance therapy is usually indicated since the leukemic process usually exacerbates promptly when mercaptopurine is stopped The starting dose of 2 5 mg per kilogram may not be tolerated indefinitely and the blood count should be taken at weekly intervals until a satisfactory maintenance dose is established Mercaptopurine is particularly indicated in pa-

ment of choice will depend on the patient's clinical situation and the physician's facilities and experience It is important to select a therapeutic agent which will cause the least interference with the patient's normal activities, and to avoid a regimen which tends to produce invalidism One of the most satisfactory methods of treatment is splenic irradiation, a single course can produce remissions of 6 months or longer in responsive cases There are a number of drugs which are useful also

Polyfunctional Alkylating Agents—These are a number of different agents which have two or more reactive alkylating groups, each alkyl group capable of being introduced in place of an active hydrogen into many organic and inorganic molecules While these agents react with a great number of components of biologic systems they appear to have a special affinity for nucleic acids Desoxyribonucleic acid appears to be the particularly vulnerable component of the cell as far as continued cellular proliferation is concerned

The polyfunctional alkylating agents presumably act by interfering with the formation of new cells in both normal and neoplastic tissues in the normal animal these agents are specifically injurious to the blood forming organs and the intestinal lining which are composed of cells which divide frequently The polyfunctional alkylating agents also cause involution of lymphatic tissue In man, also, these agents produce bone marrow depression with leukopenia, thrombocytopenia and bleeding manifestations and anemia

At toxic doses these effects usually appear 2 to 3 weeks after a course of treatment and if the patient survives, the peripheral blood picture returns to normal within 2 to 3 weeks When recovery is complete, another course of treatment can be given if indicated without appreciable cumulative bone marrow toxicity In patients with impaired marrow function due to disease however, therapeutic doses may cause prolonged bone marrow depression

These agents may be given as intermittent courses, or by continuous administration Intermittent therapy is usually safer, since the blood picture has recovered before a second course is given Continuous therapy requires precise and regular dosage control with frequent blood studies particularly if it is necessary to increase the dose in resistant patients in the hope of producing a more satisfactory response Poorly controlled maintenance therapy may result in cumulative and severe bone marrow damage, since the evidences of bone marrow depression may continue to evolve for 2 to 3 weeks after the drug is stopped The polyfunctional alkylating agents often are given to the point where appreciable bone marrow depression is produced in order to obtain a therapeutic response, and dosage must be adjusted to the drug used, the type of neoplasm, and the stage of the disease

Although the polyfunctional alkylating agents have similar cytotoxic actions they differ in their acute pharmacologic effects Nitrogen mustard, for example, produces nausea and vomiting by central action shortly after administration, whereas the ethylamines rarely do so Some are readily tolerated by mouth, whereas others cause nausea and vomiting

The efficiency of absorption by the oral route varies among these drugs and from patient to patient, and more rapid treatment and precise dosage control can be achieved by administering the drugs intravenously, when possible These are considerations in the selection of these agents for clinical use

cause a prompt fall in the leukocyte count and regression of enlarged nodes, if this occurs, further treatment is withheld for several weeks If there is no definite hematologic response to this trial dose, on the following week 2 5 mg on 2 successive days may be given *In some cases it may take 20 to 40 mg over a 2 month* period to produce a satisfactory response In some cases a complete *hematologic* remission may occur, in that all signs of the disease disappear for many months and sometimes years

A complete remission is not an essential objective of TEM therapy, however, since often a vigorous attempt to lower the leukocyte count to normal levels may cause severe bone marrow depression Once clinical improvement has occurred the regular TEM administration is discontinued, and single doses of 2 5 to 5 mg are given at intervals thereafter if the leukocyte count begins to rise or lymph nodes enlarge After prolonged TEM therapy, a responsive patient may begin to develop a fall in hemoglobin level and platelet count, while the lymphocyte count remains elevated TEM should be discontinued in these resistant patients, and other forms of treatment employed

In hospitalized patients TEM may be started *intravenously at a dose of* 0 02 mg per kilogram (1 mg in the 50 kilogram individual) and further dosage determined *by periodic blood counts*

Chlorambucil —Chlorambucil (Leukeran) is a polyfunctional alkylating agent as acceptable as TEM in chronic lymphocytic leukemia It is usually well tolerated, although occasional patients may complain of nausea and vomiting The initial daily dose is 0 05 to 0 1 mg per kilogram daily (2 to 6 mg) This is given each day, and dosage is regulated by weekly blood counts If the leukocyte count falls the drug is temporarily discontinued but if it is unchanged after three weeks the dosage may be increased When the desired clinical response is obtained, chlorambucil should be stopped and restarted when signs of renewed activity of the disease appear

The other polyfunctional alkylating agents have no special role in chronic lymphocytic leukemia

Adrenal Steroids —These drugs are extremely useful in selected situations in chronic lymphatic leukemia In patients who are refractory to TEM and have a lowered hemoglobin level with thrombocytopenia and bleeding prednisone, 50 mg *per day, may cause a prompt rise in* hemoglobin and platelet count and a decrease in the size of enlarged nodes, liver, and spleen The leukocyte count may rise abruptly when treatment is started, a not undesirable sign and then fall gradually on continued treatment If a favorable result occurs, the prednisone dose is reduced in 2 to 3 weeks *Patients have been maintained for long periods on doses* as small as 10 mg per day

Once a patient has responded, it is advisable to continue maintenance doses of prednisone indefinitely Distressing complications of continuous high doses of prednisone may be acute or resistant *infections and steroid* induced diabetes During periods of infection an increased dose of prednisone is often indicated and when diabetes occurs the dose may be lowered

In another complication of chronic lymphocytic leukemia, acquired hemolytic anemia, prednisone begun at 25 mg per day *usually causes prompt* hematologic

tients who have become refractory to the alkylating agents and radiation, sin may produce a separate period of improvement Patients in the terminal stag the disease should receive an adequate trial of Purinethol

6 Chloropurine and 6 thioguanine are effective, but have no therapeutic vantage over mercaptopurine

Miscellaneous Compounds —Other agents which have been used in chron myelocytic leukemia but offer no particular advantages are given here

AMETHOPTERIN —At near toxic doses amethopterin will reduce the leukocyt count but it rebounds promptly as soon as the drug is stopped

FOWLER'S SOLUTION —A 1 per cent solution of potassium arsenite is sometime used as a mild suppressive in early cases of chronic myelocytic leukemia, but its activity is weak compared to other agents The dosage sequence is 3 drops, 3 times daily and this is increased at the rate of 1 drop per dose per day until a maximum total of 20 drops 3 times daily is reached unless evidences of toxicity appear or a marked fall in the leukocyte count intervenes The dose is then reduced to a maintenance level

URETHAN While urethan produces excellent results in some cases, its use may be associated with nausea and vomiting drowsiness and occasionally hepatitis, and it offers no special therapeutic advantages over the available drugs

COLCHICINE ANALOGUES —The most prominent colchicine analogue used in chronic myelocytic leukemia is demecolcin The daily dose is 5 to 10 mg by mouth While this dose is well tolerated and produces a fall in the leukocyte count and clinical improvement demecolcin does not appear to be effective in patients resistant to other forms of treatment

ADRENAL STEROIDS —Prednisone is of little value in chronic myelocytic leukemia and in some instances it seems to aggravate the disease In the terminal acute stage 100 mg of prednisone daily may reduce bleeding manifestations although it has not produced any important hematologic remissions

RADIOACTIVE PHOSPHORUS —Radioactive phosphorus (P^{32}) will produce satisfactory remissions in the responsive stage of chronic myelocytic leukemia It does not appear to offer any advantage over Myleran or x ray and technically its use is more complicated

Chronic Lymphocytic Leukemia

This disease frequently runs a prolonged and relatively benign course Treat nent should be conservative since premature or excessive therapy may result in erious complications more disabling than the disease itself In the early and rela vely asymptomatic stages of the disease treatment is not indicated If localized largement of the spleen liver or lymph nodes causes difficulties, small doses of rays to these areas may be the most satisfactory procedure In active sympto tic disease several drugs are of definite value

TEM —The initial drug of choice is TEM (triethylene melamine) Chronic phatic leukemia may be extremely sensitive to the polyfunctional alkylating nts (both the excessive lymphocytes and the normal blood forming cells) Th t must be given cautiously the initial single oral dose is 2 5 —

cause a prompt fall in the leukocyte count and regression of enlarged nodes if this occurs further treatment is withheld for several weeks *If there is no definite* hematologic response to this trial dose, on the following week 2 5 mg on 2 successive days may be given In some cases it may take 20 to 40 mg over a 2 month period to produce a satisfactory response *In some cases a complete hematologic* remission may occur, in that all signs of the disease disappear for many months and sometimes years

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improvement The dose is then reduced to maintenance levels and continued indefinitely The other adrenal steroids offer no advantage over prednisone

Miscellaneous Compounds —Amethopterin, mercaptopurine, and azaserine are of no value Colchicine, urethan, and Fowler s solution exhibit irregular and uncertain effects and there is no indication for their use While radioactive phosphorus is an effective agent it is less convenient to use than the chemicals available

Monocytic Leukemia

This is a particularly difficult form of leukemia to manage, and it usually runs an acute course Mercaptopurine appears to be the agent of choice and it should be given an adequate trial Patients responding and then relapsing on mercaptopurine merit a trial of amethopterin In the more chronic varieties of monocytic leukemia busulfan may produce considerable symptomatic improvement The adrenal steroids are of no specific value

Hodgkin s Disease

Hodgkin s disease presents a variety of clinical pictures, from the localized and slowly progressive to the generalized and symptomatic forms The appropriate treatment will depend on the stage and extent of the disease, the rate of progression, and the response to previous therapy X ray therapy is the most important method of treatment at all stages of the disease, and it should not be neglected Chemotherapeutic agents are useful in the disseminated form of the disease with systemic symptoms Fever itching, anorexia, and weakness may be rapidly alleviated sometimes within 24 to 48 hours after treatment With intermittent therapy, improvement usually lasts for 6 to 10 weeks, and then another course can be given By proper maintenance therapy, with brief interruptions, these periods of symptomatic relapse may be prevented While the available drugs do not produce a general and substantial increase in survival time, they are important in prolonging comfortable and useful life

Polyfunctional Alkylating Agents —Nitrogen mustard (Mustargen), TEM and chlorambucil have their individual advantages in treatment

Nitrogen Mustard —This is the drug of choice in hospitalized patients, in whom prompt treatment is indicated The drug is dissolved in 10 ml of saline to make a 1 mg per milliliter solution, and the appropriate dose is injected into the tubing of a running intravenous infusion of physiologic saline The usual dose is 0 4 mg per kilogram given in a single dose, or divided into 2 to 4 single daily doses This dose is well tolerated when no evidence of bone marrow depression is present but in advanced cases with impaired marrow function, or in patients who have already received repeated courses of a polyfunctional alkylating agent, it is safer to give a smaller initial dose of 0 2 mg per kilogram If the therapeutic response is inadequate, further dosage may be given within 1 to 2 weeks if a satisfactory blood picture is maintained In some cases by cautious but persistent treatment to the point of a moderate leukopenia and thrombocytopenia a satisfactory temporary therapeutic response may be achieved

Nitrogen mustard may induce thrombophlebitis in the injected vein, particularly if venous pressure is high. Extravasation results in a painful area of induration, which may sometimes slough. Nausea and some degree of vomiting is a common consequence of each intravenous dose of nitrogen mustard. It may occur ½ hour to 8 hours after the injection and subsides in a few hours. Nausea and vomiting may be alleviated by giving nitrogen mustard late in the afternoon and sedating the patient for the night. One routine procedure is to administer sodium phenobarbital, 100 mg. intramuscularly, shortly after treatment, and to repeat the dose once if vomiting persists, with Thorazine, 25 mg. intramuscularly, given in 4 hours if necessary.

The advantages of nitrogen mustard are that the dosage is well established and the therapeutic effectiveness of a polyfunctional alkylating agent in a specific patient can be promptly assessed. Furthermore, the optimal therapeutic dose of nitrogen mustard can be more precisely controlled when an alkylating agent is used in combination with x-ray therapy.

TEM.—This drug, as an alternative polyfunctional alkylating agent, can be given orally or intravenously. The oral dose ranges from 5 to 10 mg. in divided doses during the first week, and the average tolerated dose during the first month of treatment is 20 to 40 mg. TEM can cause severe bone marrow depression, and it must be used with care. If an adequate response occurs, the patient may be maintained by intermittent doses at 2- to 4-week intervals, or TEM may be restarted when signs of relapse appear. The intravenous dose of TEM is 0.04 mg. per kilogram daily for 3 doses; this is as effective as nitrogen mustard and TEM is less likely to produce nausea and vomiting.

Chlorambucil.—Chlorambucil is given orally and is well tolerated. In contrast to the intermittent dosage used with TEM, chlorambucil is given daily at an initial dose of 0.1 to 0.2 mg. per kilogram (6 to 12 mg.). The blood count is followed at weekly intervals, and if it is not depressed and the therapeutic response is inadequate, the dose may be increased to 0.3 or 0.4 mg. per kilogram. Bone marrow depression is the principal hazard from persistent therapy, and we prefer continuing the drug until a satisfactory clinical response occurs or a worrisome fall in the leukocyte and platelet count begins; the drug is then stopped, and restarted, in the former case, when signs of relapse occur.

The other polyfunctional alkylating agents appear to offer no advantage over nitrogen mustard, TEM, and chlorambucil.

Adrenal Steroids.—Prednisone is rarely of specific value in Hodgkin's disease. It is usually effective, of course, in acquired hemolytic anemia which sometimes complicates Hodgkin's disease. Doses of 10 to 25 mg. per day may be sufficient to control the process. In the advanced stages of the disease, prednisone may be useful as a supportive agent, in reducing fever and in improving the patient's appetite and outlook. When pancytopenia is present, possibly as a consequence of an enlarged spleen, prednisone 50 mg. per day may improve the blood picture. If a response occurs, the dose should be reduced to the lowest level which still maintains the therapeutic response. Prednisone should not be used early in the disease; its use is not often rewarding, and prolonged therapy at high doses may introduce its own complications.

improvement The dose is then reduced to maintenance levels and continued indefinitely The other adrenal steroids offer no advantage over prednisone

Miscellaneous Compounds—*Amethopterin, mercaptopurine, and azaserine* are of no value *Colchicine* urethan and Fowler s solution exhibit irregular and un certain effects and there is no indication for their use While radioactive phos phorus is an effective agent it is less convenient to use than the chemicals available

Monocytic Leukemia

This is a particularly difficult form of leukemia to manage, and it usually runs an acute course Mercaptopurine appears to be the agent of choice and it should be given an adequate trial Patients responding and then relapsing *on mercapto purine* merit a trial of *amethopterin* In *the more chronic varieties of monocytic* leukemia busulfan *may produce considerable symptomatic improvement* The adrenal steroids are of no specific value

Hodgkin's Disease

Hodgkin s disease presents a variety of clinical pictures, from the localized and slowly progressive to the generalized and symptomatic forms The appropriate treatment will depend on the stage and extent of the disease, the rate of progres sion and the response to previous therapy X ray therapy is the most important method of treatment at all stages of the disease, and it should not be neglected Chemotherapeutic agents are useful in the disseminated form of the disease with system c symptoms Fever, itching, anorexia and weakness may be rapidly allevi ated sometimes within 24 to 48 hours after treatment With intermittent therapy improvement usually lasts for 6 to 10 weeks, and then another course can be given By proper maintenance therapy, with brief interruptions, these periods of symp tomatic relapse may be prevented While the available drugs do not produce a general and substantial increase in survival time, they are important in prolonging comfortable and useful life

Polyfunctional Alkylating Agents—Nitrogen mustard (Mustargen) TEM and chlorambucil have their individual advantages in treatment

NITROGEN MUSTARD—This is the drug of choice in hospitalized patients, in whom prompt treatment is indicated The drug is dissolved in 10 ml of saline to make a 1 mg per milliliter solution and the appropriate dose is injected into the *tubing of a running intravenous infusion of physiologic saline* The usual dose is 0 4 mg per kilogram given in a single dose or divided into 2 to 4 single daily doses This dose is well tolerated when no evidence of bone marrow de pression is present but in advanced cases with impaired marrow function, or in patients who have already received repeated courses of a polyfunctional alkylating agent it is safer to give a smaller initial dose of 0 2 mg per kilogram If the therapeutic response is inadequate, further dosage may be given within 1 to 2 weeks if a satisfactory blood picture is maintained In some cases by cautious but persistent treatment to the point of a moderate leukopenia and thrombocytopenia a satisfactory temporary therapeutic response may be achieved

The mechanism of action of urethan is not known, it is rapidly metabolized, ıd it has been suggested that it acts as an antimetabolite An adequate trial of ethan is indicated in patients with disseminated multiple myeloma, with bone arrow involvement, hyperglobulinemia, and anemia It may take 2 or more onths before a favorable response occurs, and treatment should be persistent and ntinuous if the patient's condition does not continue to deteriorate About 15 35 per cent of patients with multiple myeloma obtain significant hematologic ıprovement on urethan

Adrenal Steroids—Prednisone may produce prompt relief of pain, a fall in rum protein, and general improvement in about 30 per cent of patients The ual dose is 50 to 100 mg per day, and if a satisfactory response occurs the dose decreased Prednisone is generally used in patients with conspicuous symptoma logy If prednisone is begun simultaneously with urethan, and if immediate im ovement occurs due to the prednisone, the dosage should be reduced so that e continuing effects of urethan can be evaluated

Miscellaneous Drugs—Stilbamidine has produced no consistent response in ultiple myeloma The polyfunctional alkylating agents are generally without value ıey have been combined with urethan in some cases, but the additional benefit ›m this combination has not been demonstrated Radioactive iodine and radio- tive phosphorus have also been used with inconsistent results

ırcinoma of the Breast

Drugs have no place in the management of resectable cancer of the breast recurrent or metastatic breast cancer alterations in the hormonal balance of the st may cause temporary regression of the cancer for periods of 6 to 12 months d longer The present trend in treatment is to alter hormone balance by the ɪoval of endocrine glands—the ovaries, the adrenals, and the pituitary In ›menopausal patients with breast cancer, oophorectomy or adequate radiation stration gives a higher percentage of objective regression of disease than andro n therapy, and patients who respond to ovariectomy can expect, when relapse curs, a period of further improvement from adrenalectomy, hypophysectomy, or ›m androgens A treatment program must be designed for each patient, and ›rapeutic measures applied in a planned sequence so that their effectiveness can evaluated and the indications for the next therapeutic step established The lowing drugs are used in recurrent and advanced breast cancer

Androgenic Hormones—These are given principally to patients who are pre- nopausal or less than 10 years postmenopausal The drug produces objective provement in approximately 20 per cent of patients for periods of 4 to 10 months longer An adequate therapeutic trial should be continued for 2 months or ıger if the patient is not deteriorating If objective improvement occurs, andro ıs are continued and when relapse occurs under treatment, the drug is stopped metimes a patient who responds and then becomes refractory to androgen therapy ll have another period of remission when the drug is stopped

Androgens apparently act on breast cancer by antagonizing estrogens and by ıbiting the function of the pituitary In the presence of an unfavorable hor-

Miscellaneous Agents—Amethopterin and mercaptopurine have not proved useful in Hodgkin's disease Butazolidin, colchicine, and azaserine sometimes alleviate fever briefly, but they are not often effective Actinomycins C and D may reduce enlarged nodes and fever, but these antibiotics are unusually toxic (nausea, vomiting oral lesions, enteritis, alopecia, dermatitis, and some evidence of bone marrow depression), and they appear to have no therapeutic advantages over the polyfunctional alkylating agents

Lymphosarcoma

Lymphosarcoma, while it is closely allied to Hodgkin's disease and in many cases parallels its clinical course, shows even more extreme variations of clinical behavior in individual cases and in its response to therapy X ray therapy is the major and most universally effective form of treatment Nitrogen mustard, TEM, and chlorambucil are occasionally useful They should be started cautiously since in some cases lymphosarcoma may be as sensitive to these agents as the occasional patients with chronic lymphatic leukemia These agents are administered according to the same principles discussed for Hodgkin's disease, but generally they have not proved as effective Prednisone may prove very beneficial in some cases of lymphosarcoma, as it is in chronic lymphatic leukemia, and it merits an earlier and more persistent trial than is indicated in Hodgkin's disease This is particularly recommended in patients with fever and hematologic disturbances no longer suitable for treatment with x-rays or nitrogen mustard The initial dose is 50 mg per day, and it is lowered in responsive cases to maintenance levels in some cases a dose of 10 mg daily may sustain a satisfactory remission

Lymphosarcoma in children may respond to the agents used in childhood leukemia, and in the generalized stage of the disease, with or without bone marrow involvement, adequate trials of mercaptopurine, amethopterin, and prednisone are indicated

Multiple Myeloma

Multiple myeloma is not highly responsive to available chemotherapeutic agents Local disease which produces pain, usually due to bone involvement, is best treated by local radiation Urethan is the drug of choice Urethan may be made up in a 10 per cent solution in distilled water for intravenous use For oral use we prefer the 25 per cent solution of urethan, since there is some question about the efficiency with which urethan is liberated from enteric coated capsules in the gastrointestinal tract The usual dose is 2 to 4 Gm (2 to 4 teaspoonfuls) daily It is taken before meals Dosage should be carefully regulated by repeated blood counts since the most important toxic effect of continuous therapy is bone marrow depression In many cases it is desirable to produce a significant leukopenia in order to achieve the maximum possibility of a hematologic remission

About 50 per cent of patients complain of nausea and vomiting or drowsiness, and the dose of urethan should be reduced, and various stratagems tried to make the urethan tolerable In rare cases, severe hepatic injury has been associated with urethan administration

Adrenal Steroids—Adrenal steroids will occasionally be effective in advanced breast cancer This may be used in large doses (prednisone, 100 mg per day), which may cause brief objective regressions of disease, even in patients not responding to alterations in sex hormone balance, and as a supportive measure (15 mg per day) In hypercalcemia due to metastatic disease, prednisone frequently reduces the serum and urinary calcium levels Prednisone may promptly alleviate the neurologic manifestations of cerebral metastases from breast cancer

Polyfunctional Alkylating Agents—Ordinarily these agents are of little value in breast cancer In advanced cases, however, a course of nitrogen mustard may alleviate dyspnea due to pulmonary metastases and neurological signs due to cerebral metastases I prefer to use nitrogen mustard, 0 4 mg per kilogram, because the response, if it occurs, will be prompt Nitrogen mustard is also given intrapleurally for recurrent pleural effusions

DON—This drug does not have an established role in the management of breast cancer DON has corrected hypercalcemia due to osseous metastases in over 50 per cent of the treated patients The usual dose of DON is 0 1 to 0 2 mg per kilogram daily by mouth, and it can be given parenterally at the same dosage Treatment may be started at larger doses in acute situations Subsequent dosage is regulated by the appearance of redness of the tongue and oral ulcerations the earliest manifestations of toxicity DON is also used in combination with mercaptopurine the latter is usually given at a dose of 1 5 mg per kilogram daily

Maintenance Therapy Following Removal of the Adrenals or Hypophysis—Following complete adrenalectomy, the patient is usually maintained on oral cortisone, 37 5 to 50 mg per day, divided into 3 doses, and fludrocortisone, 0 1 mg per day The latter is used in preference to desoxycorticosterone (DOCA) During periods of stress, the dose of cortisone must be increased After hypophysectomy the patient is usually maintained on oral cortisone, 37 5 mg per day, and desiccated thyroid, 120 mg per day Diabetes insipidus is sometimes a complication of hypophysectomy Pitressin tannate in oil given by intramuscular injection (2 to 5 units every 2 to 5 days), or posterior pituitary powder, 3 to 4 snuffs per day, usually provides adequate control

Quantitative aspects of replacement therapy are necessarily determined separately for each patient

Prostate Cancer

The treatment of choice in nonresectable carcinoma of the prostate is combined castration and estrogen administration This procedure seems to provide better control of the disease and extend the survival time longer than either procedure alone Castration or estrogen therapy alone can produce satisfactory remissions however, the response to castration occurs more quickly, usually within 48 hours as compared to 10 days to 3 weeks Patients who have become refractory to estrogens may show a second period of improvement after castration castration relapses do not respond as well to estrogen therapy Hormonal control measures produce benefit in 70 to 80 per cent of the patients treated and objective regression of local

monal environment, some tumors dependent for their maximal growth on estrogenic stimulation will temporarily regress

The consequences of large doses of androgens in women are well known They include signs of masculinization—deepening of the voice, hirsutism and acne—increased libido, perineal itching, and fluid retention In patients with some degree of cardiac impairment fluid retention may precipitate heart failure These patients should be placed on a low salt diet and receive periodic injections of a mercurial diuretic Occasionally in patients with osseous disease, androgen therapy may exacerbate the disease and produce an acute episode of hypercalcemia This possibility should be held in mind during the initiation of androgen therapy

TESTOSTERONE —Testosterone propionate is the drug of choice It is available for intramuscular injection and the recommended dose is 100 mg, 3 times weekly

Two androgenic compounds are effective orally 17 methyl testosterone (methyl testosterone) is effective by mouth and the daily dose equivalent to the parenteral testosterone propionate schedule is 200 mg daily given in divided doses The drug is more expensive than testosterone propionate and it is not always certain that the patient is taking the full dose regularly Fluoxymestrone (Halotestin) appears to be as effective as parenteral testosterone propionate at a dose of 20 mg per day

OTHER ANDROGENS —There are other androgenic steroids available including long acting suspensions for intramuscular injection There is no satisfactory clinical evidence that at comparable therapeutic doses one androgen is less virilizing or more effective against breast cancer than the others Depot androgens may be dangerous because the release of the drug is continuous and uncontrollable and androgens may sometimes exacerbate the disease

Estrogenic Hormones —These are used principally in patients 10 years or more postmenopausal They produce objective improvement in approximately 30 per cent of patients for periods of 6 to 12 months or longer An adequate trial should continue for at least 2 months if the disease is not progressing, and in responsive patients the drug is continued until relapse occurs

Estrogens apparently act on breast cancer by inhibiting the pituitary gland Thus there are instances where a brief exacerbation of the disease is induced at the onset of estrogen therapy (direct tumor stimulation) to be followed by tumor regression (pituitary inhibition) In hypophysectomized patients known to have estrogen dependent tumors, estrogen administration has not stimulated tumor growth

Excessive estrogen activity in women causes fluid retention enlargement of the breasts and uterine bleeding, which usually appears when the drug is stopped When uterine bleeding occurs during estrogen therapy, it may cease when the dose is increased In males estrogens produce enlarged tender breasts and diminished libido

Diethylstilbestrol is the drug of choice The usual dose is 15 mg per day (5 mg 3 times daily) Stilbestrol may occasionally cause nausea and vomiting An alternative preparation is ethinyl estradiol, which is more active than stilbestrol by weight The usual dose is 3 mg daily (1 mg, 3 times daily) Estradiol benzoate is available for intramuscular administration, the dose is 5 mg, 3 times weekly

ocalized radiotherapy One important indication for a chemotherapeutic agent the superior vena cava syndrome (consisting of swelling of the neck face and rms elevated venous pressure in the arms and dyspnea) This may be relieved romptly in 80 to 90 per cent of the cases by nitrogen mustard In this situation is advisable to try to prolong the response by local irradiation of the tumor

Polyfunctional Alkylating Agents—Nitrogen mustard (Mustargen) is the eatment of choice The usual dose, given intravenously, is 0 4 mg per kilogram nd in patients who have a blood picture within normal limits I prefer giving it s a single injection These patients usually tolerate larger doses of nitrogen mus ard and if the expected response has not occurred a second dose can be given in to 3 weeks if the blood count is not depressed The usual duration of improve ent is 4 to 6 weeks

Nitrogen mustard is preferred to the other alkylating agents because an ade uate dose can be given and the maximum response is obtained promptly My xperiences with the oral alkylating agents have not been satisfactory, since treat ent is given over a prolonged period and it is more difficult to administer the aximum tolerated dose safely

Adrenal Steroids—Cortisone is used as a supportive agent in advanced lung ancer Adrenal metastases occur frequently in lung cancer although a true drenocortical deficiency state is difficult to demonstrate Cortisone 50 mg per ay divided into 2 doses, may cause symptomatic improvement, but there is no idence of any direct effect on the disease

arcinoma of the Ovary

In advanced ovarian cancer, with large pelvic masses ascites or intestinal ostruction the polyfunctional alkylating agents may sometimes provide consider ble temporary relief Approximately 30 per cent of the patients have obtained ojective evidences of tumor regression and clinical benefit, averaging 2 to 4 months nd sometimes longer

TEM (triethylene melamine) is the drug of choice Generally, the hospitalized atient is given a complete course of treatment intravenously, 0 04 mg per kilo am in 3 daily doses If a favorable response occurs, the patient is maintained n oral TEM, at doses of 2 5 to 20 mg per month Long continued therapy can ad to bone marrow depression, and the administration of TEM should be con olled carefully

Nitrogen mustard is probably equally satisfactory for intravenous therapy and e patient also can be maintained on chlorambucil (Leukeran), 0 1 to 0 2 mg per logram by mouth The other alkylating agents have no advantage over TEM, trogen mustard and chlorambucil in ovarian cancer

In advanced cases prednisone, 15 to 25 mg per day, may be of supportive lue although it does not appear to influence the disease directly

arcinoma of the Thyroid

Carcinoma of the thyroid is generally treated first by surgery Of those with nresectable or metastatic cancer, 10 to 20 per cent have tumors which can be

disease and metastases in a substantial number of cases They unquestionably prolong survival time

Diethylstilbestrol is the drug of choice The usual dose is 1 0 mg , 1 to 3 times daily Although these small doses are adequate to produce a response, larger doses have been used If stilbestrol is not well tolerated ethinyl estradiol is an effective alternative The dose is 0 1 mg , 1 to 3 times daily Treatment is continued during the period of improvement There are other estrogenic substances available which are effective in prostatic cancer, but they offer no advantages over diethylstilbestrol

Prednisone may occasionally produce brief periods of improvement in patients refractory to the estrogenic hormones The usual dose is 50 to 100 mg each day in divided doses

Adrenalectomy and hypophysectomy have proved far more useful in breast cancer although occasional patients with prostatic cancer have responded In general these operative measures are not recommended

Choriocarcinoma

Metastatic choriocarcinoma in the female is a rare type of cancer It is composed of cells of fetal origin and thus its cells, immunologically, are not entirely identical with its maternal host It has proved responsive to chemotherapeutic agents

Folic Acid Antagonists —The treatment and drug of choice is amethopterin (Methotrexate) One suggested schedule of treatment is 25 mg of amethopterin by mouth daily for 5 days This dosage schedule is repeated at intervals, after signs of toxicity from the previous course have cleared, until evidence of the disease has disappeared This dose has reduced the titer of chorionic hormone in the urine and caused remarkable clinical improvement In 27 patients 5 apparently had complete remissions and 7 partial remissions in that the only remaining evidence of disease is an elevated chorionic hormone titer Some of these patients may be free of cancer It is not certain that this large and possibly hazardous dose schedule is essential it is possible that similar results can be obtained by the use of more conventional therapy i e , 5 mg of amethopterin as an initial daily dose continued and increased at intervals until signs of oral or hematologic toxicity occur

Polyfunctional Alkylating Agents —Nitrogen mustard (0 4 mg per kilogram) has produced prolonged improvement, and one apparently cured patient has been reported Possibly the combination of nitrogen mustard and amethopterin may prove more effective

In males amethopterin, nitrogen mustard, and DON have produced no important or consistent effect in choriocarcinoma

Carcinoma of the Lung

In nonresectable, apparently localized carcinoma of the lung, and for circumscribed metastases radiotherapy offers the best chance for prolonged control of the disease In patients with extensive pulmonary disease, with widespread metastases, chemotherapeutic agents may provide brief periods of relief, with reduction in cough, sputum, pain, and weakness They are often given in conjunction with

rivative of nitrogen mustard (Melphalan, Sarcolysin) is reputed to produce improvement in seminomas, as have Thio-TEPA in melanoma and E39 (an ethylenimine derivative) in gastric cancer It is very probable that all these agents have the same mechanism of action, and the responses reported in individual patients from a particular derivative could have been produced by adequate doses of any one of the active polyfunctional alkylating agents.

Adrenal Steroids —Cortisone, prednisone, and related steroids are occasionally of supportive value in patients with advanced cancer, but they do not produce any specific effects on the disease *Their general use is not recommended*

Actinomycin D —This agent has produced regression of pulmonary metastases from Wilms's tumors in children, the consistency of this response has not been *established* The usual dose is 0 015 mg per kilogram (0 3 mg in the 20 kilogram child) daily for 4 to 5 days, and treatment may be repeated when the signs of toxicity clear

Regional Chemotherapy

Polyfunctional alkylating agents have been given by intra arterial and by intrapleural injection in order to produce a more drastic effect on local disease While many derivatives have been tried, nitrogen mustard is the drug of choice Experience has led us to use intra arterial injection only in the pelvic area A wide-bore needle is introduced into the femoral artery and a polyethylene catheter threaded through it up to the desired level of the aorta A single dose of 0 4 mg per kilogram of nitrogen mustard is injected slowly into the tubing, and the catheter is then withdrawn The pelvic organs undoubtedly receive, through their arterial supply, a higher concentration of nitrogen mustard, but this route of administration nevertheless also produces systemic effects similar to those following intravenous injection The procedure has produced temporary improvement in carcinoma of the cervix and ovary and in lymphosarcoma in the pelvic region Tumor regression has occurred, uremia due to ureteral compression has been relieved ascites cleared and leg edema and pelvic pain diminished

In recurrent pleural effusions due to cancer, nitrogen mustard has produced prolonged control in about 25 per cent of the patients treated, the most consistent responses have occurred in effusions due to breast and lung cancer After rapid recurrence of a pleural effusion has been demonstrated, the usual procedure is to withdraw the fluid almost completely and to inject 0 4 mg per kilogram of nitrogen mustard in 20 ml of saline into the residual fluid The patient then breathes deeply and sits up and lies down several times to distribute the drug In some patients this dose is readily absorbed from the pleural space and induces the usual systemic effects of nitrogen mustard A similar technique is used for the intraperitoneal injection of nitrogen mustard in patients with recurrent ascites

Radioactive Gold (Au^{198}) —Radioactive gold is now widely used in recurrent pleural effusion and ascites In the case of pleural effusion, it does not appear to be more effective than nitrogen mustard The usual intraperitoneal dose is 80 to 120 millicuries, injected after the major portion of the ascitic fluid has been withdrawn

shown to concentrate iodine, as indicated by uptake studies with tracer doses of radioactive iodine. In these patients the ability of the cancer to concentrate iodine can be enhanced by removing or destroying the normal thyroid (by surgery or radioactive iodine) and then pretreating the patient with an antithyroid drug.

Methimazole (Tapazole) is the drug of choice. The usual dose is 15 mg., 4 times daily (60 mg. per day), for 1 to 2 months. Tapazole is then stopped for 2 days and a tracer dose of radioactive iodine is given to determine whether there is sufficient uptake to warrant a therapeutic dose. The dose of radioactive iodine, calculated from the uptake of the tracer dose, is in the range of 50 to 500 millicuries, and is given orally. About 50 per cent of the patients selected for treatment obtain clinical benefit, due to destructive effects of radiation from the radioactive iodine on the neoplastic cells.

At present, I^{131} (8 day half-life, beta and gamma emitter) is preferred, but in selected situations the use of I^{132} and I^{133} has been suggested. These latter isotopes are difficult to obtain, and their therapeutic advantages over I^{131} have not been demonstrated.

The administration of desiccated thyroid (0.2 to 0.3 Gm. per day), thyroxine (0.4 mg. per day), or triiodothyronine (100 to 200 mcg. per day) by mouth has been reported to produce clinical benefit in occasional patients with extensive metastatic cancer; one of these preparations may be tried in patients resistant to other forms of treatment.

Neuroblastoma

Metastatic neuroblastoma may undergo spontaneous regression in 5 to 10 per cent of all cases. Vigorous treatment with x-rays, nitrogen mustard, adrenal steroids, and antimetabolites may inhibit the progression of the disease, and in some cases the patient may survive long enough to obtain a spontaneous regression. In this condition, vigorous, persistent, and hopeful therapy is indicated.

Miscellaneous Types of Cancer

In general, chemotherapeutic agents have not been effective in most forms of cancer, including carcinomas of the esophagus, stomach, pancreas, urinary bladder, rectum, large bowel, cervix, in brain and bone tumors, and in melanomas. This cannot be a categoric statement, since in rare instances these tumors have been found to show a transient response to a chemotherapeutic agent. These reports can be explained by an unusual metabolic pattern of the tumor rendering it responsive to a drug, by a temporary spontaneous regression, or by the natural history of the disease. While these isolated responses are of interest, we are primarily concerned here with drugs which exhibit a consistent effect on certain forms of cancer. Agents that have been associated with rare improvement in miscellaneous types of cancer include the following.

Polyfunctional Alkylating Agents.—In rapidly progressive and anaplastic carcinomas, nitrogen mustard has caused measurable regressions in carcinomas of the stomach, uterus, and kidney, in Wilms's tumor, and in neuroblastomas and seminomas. It has relieved fever in osteogenic sarcoma. The phenylalanine de-

definite toxicity in the host in order to elicit a therapeutic response These drugs have a narrow spectrum of action in that they only affect a few of the many different forms of cancer They are not curative, and only in acute leukemia in children and in carcinoma of the prostate can chemotherapy be said to have definitely prolonged survival time The available drugs cause only temporary improvement at best, and the neoplastic cells ultimately develop resistance and continue to proliferate despite further treatment

It would be desirable to have less toxic and more specific agents with a wider spectrum of therapeutic activity The problem of cellular resistance will have to be overcome Exploration of analogues of the available types of compounds has not been rewarding, and very likely the major advances will be in discovering new classes of drugs

[Experience with cyclophosphamide (Cytoxan) is too limited for evaluation Ed]

SELECTED REFERENCES

Ackerman, L V , and Del Regato, J A Cancer Diagnosis, Treatment and Prognosis, St Louis, 1954, The C V Mosby Co

Burchenal, J H Current Status of Clinical Chemotherapy Current Research in Cancer [illegible] Report No 4 [illegible] ed by Committee on Cancer Chemotherapy of [illegible] February 1956

Burchena[illegible] kes M P, Tan C T C, Leone, L A [illegible], H W, and Rhoads, C P Clinical Evaluation of a New [illegible] ercaptopurine, in the Treatment of Leukemia and Allied Diseases, Blood 8 965, 1953

Burchenal, J H , Murphy, M L , and Tan, C T C Treatment of Acute Leukemia, Pediatrics 18 643, 1956

Conferen[illegible] and B[illegible]ological Effects of Alkylating Agents, Ann New

Creech, [illegible] ma by Isolation

Curren, [illegible] erger, C Clin

Farber, [illegible] herapy of Cancer

Galton, [illegible] kemias Advances in Cancer Research 4 [illegible]

Hertz R Bergenstal D M , Lipsett M B , Price, E G , and Hilbish, T F Chemotherapy of Choriocarcinoma and Related Trophoblastic Tumors in Women, J A M A 168 845 1958

Karnofsky, D A Chemotherapy of Neoplastic Disease New England J Med 239 226 [illegible]

Sykes, M P , [illegible] in the Management of Far A[illegible] 133, 1955

Drugs and Procedures of Recent Interest

Fluorinated Pyrimidines—The fluorinated pyrimidines including 5 fluorouracil (FU) and 5 fluorodeoxyuridine (FUDR) are under intensive clinical investigation These compounds must be given in near toxic doses in order to produce clinical benefit and temporary regressions have been observed in large bowel and breast cancers and in primary hepatomas The consistency and duration of improvement produced by these drugs are not well defined and this class of drug is still in the experimental category The drugs cannot be recommended yet for general use

Isolation Perfusion Technique—The blood supply to certain tumor bearing areas has been isolated and the area perfused for short periods with high concentrations of chemotherapeutic agents without producing serious systemic intoxication Phenylalanine mustard and nitrogen mustard as well as other agents have been used The indications and the benefits to be expected from this procedure have not been established

Intra arterial Infusion—Another technique recently described consists of the continuous intra arterial infusion of a drug to the tumor bearing area with the systemic administration of a suitable antidote to prevent systemic toxicity The drugs thus far used are amethopterin intra arterially and citrovorum factor intramuscularly to counteract the effects of amethopterin on the bone marrow and intestinal tract Regressions have been observed in carcinomas in the head and neck region but the general applicability of this method has not yet been determined

UNPROVED FORMS OF TREATMENT

The patient with advanced cancer is often desperate and seeks any possible help To take advantage of his plight many drugs or systems of treatment are being promoted and flagrantly publicized as effective or curative in advanced cancer These unproved methods irrespective of their source are being examined as they appear by trained investigators for any possible effect against cancer Anything of value will certainly be immediately confirmed and the information made available to the medical profession Meanwhile, the use by a physician of a secret mysterious irrational or shady method of treatment is obviously unjustified By recommending or sanctioning the use of these agents one adds to the reputation and income of the cancer quack The physician is cautioned to investigate carefully any claims concerning new drugs for the treatment of cancer and to insist on acceptable scientific evidence to support the claims Usually the more flamboyant the claim the scantier the scientific evidence

FUTURE OF CHEMOTHERAPY IN CANCER

No drugs available for the treatment of cancer are entirely satisfactory It is a tribute to the clinical investigators in the cancer chemotherapy field that these drugs have been examined very thoroughly and their virtues and failings clearly described The available drugs are not specific for cancer, and are injurious to some of the normal tissues of the host In many cases it is necessary to produce

definite toxicity in the host in order to elicit a therapeutic response These drugs have a narrow spectrum of action in that they only affect a few of the many different forms of cancer They are not curative, and only in acute leukemia in children and in carcinoma of the prostate can chemotherapy be said to have definitely prolonged survival time The available drugs cause only temporary improvement at best, and the neoplastic cells ultimately develop resistance and continue to proliferate despite further treatment

It would be desirable to have less toxic and more specific agents with a wider spectrum of therapeutic activity The problem of cellular resistance will have to be overcome Exploration of analogues of the available types of compounds has not been rewarding, and very likely the major advances will be in discovering new classes of drugs

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SELECTED REFERENCES

Ackerman, L V, and Del Regato, J A Cancer Diagnosis Treatment and Prognosis, St Louis 1954, The C V Mosby Co

Burchenal, J H Current Status of Clinical Chemotherapy Current Research in Cancer ... n Cancer Chemotherapy of ... 956

Burchena ... an C T C, Leone, L A ... d Rhoads C P Clinical ... in the Treatment of Leu ...

Burchena ... t of Acute Leukemia, Pedi ...

Conference on Comparative Clinical and Biological Effects of Alkylating Agents, Ann New York Acad Sc 68 657, 1958

Creech O, Jr Ryan, R F, and Krementz E T Treatment of Melanoma by Isolation Perfusion Technique, J A M A 169 339 1959

Curreri, A R, Ansfield, F J, McIver, F A, Waisman H A, and Heidelberger, C Clinical Studies With 5 Fluorouracil, Cancer Res 18 478, 1958

Farber, S, Toch, R, Sears E M, and Pinkel D Advances in Chemotherapy of Cancer in Man Advances in Cancer Research 4 1 71, 1956

Galton D A G The Use of Myleran and Similar Agents in Chronic Leukemias Advances in Cancer Research 4 73 112, 1956

Hertz R Bergenstal D M, Lipsett, M B Price E G and Hilbish, T F Chemotherapy of Choriocarcinoma and Related Trophoblastic Tumors in Women J A M A 168 845 1958

Karnofsky D A Chemotherapy of Neoplastic Disease, New England J Med 239 226 260 299 1948

Karnofsky ...

Karnofsky ...

Karnofsky ... the Treatment of Leu ...

... American Cancer So ... Service, Philadelphia

... te Combinat on Cancer ... amuscular Citrovorum

... Triethylene Melamine ... Gynec & Obst 101 ... 155, 1955

THE CHOICE OF DRUGS FOR HEMATOLOGIC DISORDERS

William McFarland, M.D., and
William Dameshek, M.D.

INTRODUCTION

As one approaches hematologic disorders from a therapeutic standpoint, it is interesting to observe that treatment in this particular branch of medicine antedates the days of Hippocrates when iron was recognized as a beneficial medicament. Also, as a result of years of curiosity and investigation regarding the blood and its abnormalities an unusual number of specific therapeutic agents is available. This fact exacts correct diagnosis in order that specific therapy may be instituted.

Since our purpose in this chapter is to discuss our preference for various therapeutic agents, as well as to present a design for their use, we wish to remind the reader of several points. First, the various clinical syndromes will be mentioned with little or no reference to the signs, symptoms, or diagnostic essentials. Second, in many cases we will not be presenting *total care* for the patient with the hematologic disorder under discussion. Third, certain conditions for which there is no known therapeutic agent may be mentioned only briefly or omitted entirely.

It should be pointed out also that the various myelodepressants, antimetabolites, and alkylating agents used in the therapy of leukemias and lymphomas are discussed in Chapter 33.

CLINICAL APPLICATIONS

For the sake of brevity, the various clinical syndromes encountered in hematologic practice and included in this chapter may be classified in three main groups: (1) cytopenic disorders, including anemias, leukopenias (particularly granulocytopenia), and thrombocytopenias, (2) myeloproliferative disorders, including polycythemia vera, granulocytic leukemia, thrombocythemia, and myeloid metaplasia, and (3) hemorrhagic disorders.

Cytopenic Disorders.—

ANEMIAS. From the practical standpoint, clinically and therapeutically we may think of the anemias as the result of defects in (1) the diet or the gastrointestinal tract, (2) the bone marrow, or (3) the blood.

lefinite toxicity in the host in order to elicit a therapeutic response These drugs have a narrow spectrum of action in that they only affect a few of the many different forms of cancer They are not curative, and only in acute leukemia in children and in carcinoma of the prostate can chemotherapy be said to have definitely prolonged survival time The available drugs cause only temporary improvement at best, and the neoplastic cells ultimately develop resistance and continue to proliferate despite further treatment

It would be desirable to have less toxic and more specific agents with a wider spectrum of therapeutic activity The problem of cellular resistance will have to be overcome Exploration of analogues of the available types of compounds has not been rewarding, and very likely the major advances will be in discovering new classes of drugs

[Experience with cyclophosphamide (Cytoxan) is too limited for evaluation Ed]

SELECTED REFERENCES

Ackerman, L V, and Del Regato, J A Cancer Diagnosis, Treatment and Prognosis, St Louis, 1954, The C V Mosby Co

Burchenal, J H Current Status of Clinical Chemotherapy Current Research in Cancer ... Committee on *Cancer Chemotherapy* of ...), February, 1956

Burchena ... ykes, M P, Tan C T C, Leone, L A ... n, H W, and Rhoads, C P Clinical ... Mercaptopurine, in the Treatment of Leu ... 53

Burchena ... C Treatment of Acute Leukemia, Pedi

Conference on Comparative Clinical and Biological Effects of Alkylating Agents, Ann New York Acad Sc 68 657, 1958

Creech, O, Jr, Ryan, R F, and Krementz, E T Treatment of Melanoma by Isolation Perfusion Technique, J A M A 169 339, 1959

Curreri, ... Clini

Farber, S ... Cancer

Galton, D ... dvances in Cancer Research 4 ... 1956

Hertz, R, Bergenstal, D M, Lipsett, M B, Price, E G, and Hilbish, T F Chemotherapy of Choriocarcinoma and Related Trophoblastic Tumors in Women, J A M A 168 845, 1958

Karnofsky, D A Chemotherapy of Neoplastic Disease, New England J Med 239 226, 260 299, 1948

Karnofsky, D A Chemical Agents Used in the Treatment of Inoperable and Far Advanced Neoplastic Disease, Monographs in Med, Series 1, pp 582 636, 1952

Karnofsky, D A, Myers, W P L, and Phillips, R Treatment of the Inoperable Pulmonary Cancer, Primary and Metastatic, Am J Surg 89 526, 1955

Karnofsky, D A, and Rawson, R W, editors *Symposium on the Medical Aspects of Cancer*, ... May, 1956

... Antagonists in the Treatment of Leu ...

... ce, sponsored by American Cancer So- ... S Public Health Service, Philadelphia, ...

... 133, 1955

Chapter 34

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Cytopenic Disorders —

ANEMIAS —From the practical standpoint, clinically and therapeutically we may think of the anemias as the result of defects in (1) the diet or the gastro intestinal tract, (2) the bone marrow, or (3) the blood

Deficiency Anemias Accordingly, the first group includes the deficiency anemias, whether the deficiency is primarily dietary or the result of defective absorption from the gastrointestinal tract or the result of increased requirement This group includes anemias resulting from deficiencies of iron vitamin B_{12} (Addisonian pernicious anemia postgastrectomy fish tapeworm infestation), other members of the vitamin B group (pellagra anemia due to *pyridoxine deficiency), and folic* acid (macrocytic anemias of sprue, steatorrhea, celiac disease, pregnancy, surgical procedures or abnormalities of the gastrointestinal tract) Treatment of this group requires administration of the *specific deficient factor with some overlapping in* the case of folic acid and vitamin B_{12} viz, most macrocytic anemias of pregnancy respond to folic acid, whereas a few may require B_{12}

Marrow Defects *The second group of anemias* is due to a *failure* on the part of the marrow to produce cells normally This group is characterized by cytopenias in the peripheral blood but the marrow may vary from a picture of hypercellularity *to one of aplasia* The bone marrow *failure* may be idiopathic in which case the anemia is termed refractory or aplastic anemia or the bone marrow failure may be secondary to known toxic or inhibiting agents such as propylthiouracil benzene heavy metals *chloramphenicol*, phenylbutazone nitrogen mustard and other chemical substances x radiation uremia infection hypothyroidism and hypersplenism Also included in this group are the myelophthisic anemias in which the marrow apparently fails because of the presence in the marrow space of abnormal cells viz, metastatic neoplasm multiple myeloma leukemia Gaucher cells lymphomas and myelofibrosis There are no specific drugs for therapy of this group of anemias except where hormonal factors are lacking as in hypothyroidism We use corticosteroids and blood transfusions in the idiopathic bone marrow failures with occasionally gratifying results The secondary group may respond to removal of the offending toxic agent if present or to treatment of the underlying infection uremia or leukemia

Blood Loss The third group of anemias results from excessive blood loss through either hemorrhage or hemolysis If due to acute hemorrhage, blood transfusions are required If due to chronic hemorrhage a nutritious diet and iron may be the only requirements in addition to treatment of the underlying cause

Hemolytic Anemias Hemolytic anemias are classified as congenital or acquired The congenital group includes congenital spherocytosis thalassemia sickle cell disease and other hemoglobinopathies There is no specific drug therapy of this group of anemias Blood transfusions are utilized as seldom as possible because of the danger of hepatitis and eventual *hemochromatosis and the individual must live* within the bounds of his established level of anemia

The acquired hemolytic anemias are immune or nonimmune, depending upon whether or not an immune mechanism can be established The immune varieties include autoimmune hemolytic anemia erythroblastosis fetalis transfusion reactions and paroxysmal cold hemoglobinuria The most important of these from the standpoint of drug therapy is autoimmune hemolytic anemia which may be idiopathic or may occur in association with a primary disease such as chronic lymphocytic leukemia lymphosarcoma or disseminated *lupus erythematosus* Corticosteroid therapy has proved quite beneficial in this disease

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Cytopenic Disorders —

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Myeloid metaplasia may occur *sui generis* or in association with polycythemia vera leukemias, lymphomas, metastatic malignancies, and others At present, there is no satisfactory drug therapy for this condition, although we occasionally use one of the alkylating agents in small doses In general, therapy is limited to blood transfusions, and when a hemolytic component is evident, splenectomy may be performed, with a resultant reduction in transfusion requirements Fortunately, the disease is rather chronic unless secondary to a malignant lesion, and affected individuals may often lead normal lives for years without any form of therapy

Hemorrhagic Disorders—A complete classification of the hemorrhagic disorders is beyond the scope of this discussion Briefly, however, hemorrhagic disorders can be considered primarily as (1) vascular, (2) platelet, (3) coagulation defects, and (4) those due to the development of a fibrinolytic defect There is frequently much overlapping, and a single defect is only rarely the cause of the entire disturbance

Vascular Defect—Of the many hemorrhagic disorders on the basis of vascular defect, most of them are benign, require no therapy, and therefore will not be discussed here The use of flavone derivatives, including rutin, in this group has been generally unsatisfactory The hemorrhagic tendency in scurvy is ordinarily due to increased vascular permeability and responds readily to the administration of vitamin C The more important anaphylactoid purpura (Henoch Schonlein purpura) and so-called "vascular pseudohemophilia" may respond to corticosteroid therapy, and treatment of these cases will be presented

Platelet Defect—Platelet deficiencies have been discussed above as cytopenic disorders

Coagulation Defect—Hemorrhagic disorders due to coagulation defects may be considered according to whether the defect is primarily in Stage I, II, or III of the coagulation mechanism Stage I deals with the thromboplastin complex and deficiencies in this group may include platelets (vide supra), antihemophilic globulin (hemophilia), plasma thromboplastin component (PTC deficiency or Christmas disease), and plasma thromboplastin antecedent (PTA deficiency) Stage II is concerned with thrombin complex, and the recognized factors of this group are prothrombin, proaccelerin (Factor V or labile factor) and proconvertin (Factor VII or stable factor) Deficiencies in this group may be congenital but more commonly result from liver disease, vitamin K deficiency secondary to biliary obstruction or antibiotic sterilization of intestinal flora, or from anticoagulant therapy with the coumarins

Fibrin Defect—Stage III of the coagulation mechanism is concerned with the conversion of fibrinogen to fibrin, and deficiencies in this stage may be congenital or acquired The mechanism of the acquired deficiency is not distinct It may be fibrinolytic as in certain cases of leukemia, carcinoma, and operative procedures on the prostate, lung, uterus, pancreas, and possibly other organs Or, the mechanism may be one of defibrinogenation, as in hemorrhagic disorders associated with abruptio placentae, retention of dead fetus, and amniotic fluid embolization Admittedly, the separation of these cases according to whether the mechanism is mainly one of fibrinolysis or defibrinogenation is arbitrary, as both mechanisms may be operative in any one case Both require rapid replacement of

The nonimmune acquired hemolytic anemias include those due to various chemical, bacterial, and protozoal agents and others occurring in association with malignancies Treatment of this group obviously requires removal of the offending toxic agent or treatment of the primary disease In addition there are the rare disturbances of paroxysmal nocturnal hemoglobinuria and thrombohemolytic thrombocytopenic purpura both of which are difficult to classify

LEUKOPENIAS —

Agranulocytosis Agranulocytosis may occur in an acute form (agranulocytic angina) or in a chronic or recurrent form The etiology of the acute form is usually the development of an unusual degree of hypersensitivity to a drug or chemical which when removed may permit recovery of the marrow and restoration of the granulocytes to normal However the etiology of the chronic or recurrent forms is more obscure and includes immune mechanisms hypersplenism and bone marrow failure from unknown causes In addition to removing toxic substances when present and the administration of antibiotics corticosteroids may occasionally be used The exact value of the steroids is difficult to assess because controls are never available but it is possible that they exert a favorable effect through inhibition of immune mechanisms

THROMBOCYTOPENIAS —A platelet deficiency may be quantitative or qualitative, the former being the most common and therefore most important Thrombocytopenia may be idiopathic in which case megakaryocytes are present in the marrow in normal or increased numbers Secondary or megakaryocytic thrombocytopenia results from bone marrow failure from any cause and in this case marrow megakaryocytes are decreased or absent Corticosteroids are helpful and occasionally curative in idiopathic thrombocytopenic purpura and cases failing to respond to steroids may respond to splenectomy Secondary thrombocytopenias obviously require therapy of the primary disease Therapy of thrombotic thrombocytopenic purpura appears to be completely ineffectual

Myeloproliferative Disorders —Under this heading we include polycythemia vera granulocytic leukemia erythroleukemia thrombocythemia and myeloid metaplasia Since the leukemias are discussed in Chapter 33 we shall be concerned here with polycythemia thrombocythemia and myeloid metaplasia

The principal danger in polycythemia vera is the increased tendency to arterial and venous thromboses resulting from the increased viscosity of the blood and the abnormally high platelet count The increased blood volume and viscosity are directly related to the increased red cell mass and treatment therefore consists of reducing this mass by phlebotomies with or without the administration of a myelo-depressant such as P^{32} This agent depresses marrow activity in general thereby limiting production of all elements including platelets In addition anticoagulants are sometimes useful temporarily until the threat of thromboses is controlled An iron deficient diet is occasionally helpful in limiting red cell production and decreasing the frequency of P^{32} administration

The rare case in which thrombocythemia is the outstanding abnormality is fraught with the danger of thromboses and paradoxically hemorrhages Therapy in these cases consists of the administration of P^{32} and temporary anticoagulant therapy until the P^{32} has effectively reduced platelet production toward normal levels

min B_{12} The corticosteroids are grouped together since it is difficult to prove a selective hematologic action of any one hormone However, we have the distinct impression that prednisone is more beneficial and can be effective with fewer side effects than the others, therefore, we use it almost exclusively at present That this policy may not continue to be justified is evidenced by the increasing reports in the literature of recalcitrant, nonhematologic conditions which failed to respond to one steroid hormone but which did respond when another was substituted This has also been our experience on rare occasions

Several of the antihemorrhagic agents listed above could also be listed as "Specifics," but it seems more convenient to think of them in connection with hemorrhagic disorders

Perhaps the two most important ancillary agents used in hematology are anti coagulants and antibiotics Their use will not be discussed in this chapter as they are discussed thoroughly elsewhere (Chapters 8 and 35), and the same fundamentals apply to their use in hematologic disorders as in other fields of medicine Of course, ancillary agents should also include all agents used in symptomatic therapy, such as sedatives, salicylates and others, but they are merely mentioned in the interest of completeness

GENERAL PHARMACOLOGIC CONSIDERATIONS

Iron —Through rather recent advances in the understanding of iron metab olism it is known that a 70 Kg man has approximately 4 to 5 Gm of iron in his body, of which 60 to 70 per cent is in hemoglobin, and most of the remainder in available iron stores Iron metabolism is virtually a closed system in which, under normal conditions, only about 1 to 2 mg of iron is absorbed and excreted daily Dietary iron occurs mainly as ferric hydroxide and loose chelates from which ferric iron is made available in the presence of an acid medium, as in the stomach This is then converted to the ferrous form by the action of reducing substances such as vitamin C and it is this ferrous form that is absorbed through the gastrointestinal mucosa of the stomach and small bowel Accordingly, therapeutic iron is adminis tered in the ferrous form, and the amount absorbed approximates 10 per cent of the iron available in the gastrointestinal tract In the presence of iron deficiency and certain other anemias, this figure is higher and supposedly accounts for the tendency for hemochromatosis to develop in patients with refractory or hemolytic anemias given iron over many years

Iron in accidental overdosage in children has resulted in vomiting, lethargy, coma, and death In the usual therapeutic doses, it may cause abdominal cramps with diarrhea or constipation Given intravenously, there may be reactions con sisting of flushing, chest and back pain, hypotension, tachycardia, and syncope Fortunately this route of administration has been indicated rarely, if at all, since the advent of an effective iron dextran preparation which is remarkably free of serious side effects when given intramuscularly

Vitamin B_{12} and Other Vitamins —Vitamin B_{12}, or cyanocobalamin, is a dark red, crystalline compound of highly complex chemical structure which is obtained commercially from cultures of several species of Streptomyces It occurs naturally

fibrinogen by the use of blood or plasma with the addition of concentrated preparations of fibrinogen. When a fibrinolysin can be demonstrated, corticosteroids are helpful.

THERAPY.—Therapy of hemorrhagic disorders due to coagulation defects requires replacement of the deficient factor, and the manner of replacement can be simple and all-inclusive or more complex, depending upon the urgency of the situation and whether or not specific therapeutic products are available. In other words, any bleeding disorder due to coagulation defects can be treated by the administration of fresh whole blood if there is anemia, or plasma—either fresh, fresh frozen, or lyophilized—in the absence of anemia. In fact, in any case in which hemorrhage has been severe, fresh whole blood or plasma should be combined with replacement of the specific deficient factor, because with hemorrhage a loss of other factors normally present occurs, thereby creating multiple deficiencies.

THE SEVERAL DRUGS

According to the clinical indications enumerated above, the several therapeutic agents used in hematologic disorders may be outlined as shown in Table 41.

It is obvious that a number of therapeutic agents have been omitted from this outline. For instance, we have omitted other metals such as copper, cobalt, manganese, and molybdenum, which appear to have no sound application in therapy of anemia. Liver extract is not listed as such since its activity is proportional to its content of vitamin B_{12} and will be included in the discussion of the use of vita-

Table 41. The Several Therapeutic Agents Used in Hematologic Disorders

Groups	*Agent*	*Clinical Applications*
Specifics:	Iron	Iron deficiency anemia
	B_{12} and liver extract	Pernicious anemia
		Anemia following gastrectomy
		Certain macrocytic anemias not responsive to folic acid
	Folic acid	Macrocytic anemias of sprue, steatorrhea, celiac disease, pregnancy, surgical or developmental anomalies of the gastrointestinal tract, fish tapeworm infestation
	Other vitamins (B group, C)	Pellagra, scurvy, pyridoxine deficiency
Nonspecifics:	Corticosteroids (prednisone, ACTH, cortisone)	Aplastic anemia
		Hemolytic anemia
		Idiopathic thrombocytopenic purpura
		Vascular purpura
		Fibrinolysis ?
Myelotoxic agents	P^{32}, Myleran, etc. (excluded are other myelotoxic agents discussed in Chapter 33)	Polycythemia vera
		Thrombocythemia
Antihemorrhagic agents	Platelets	Thrombocytopenia
	Antihemophilic globulin	Hemophilia
	Serum	PTC deficiency
	Vitamin K	Prothrombin deficiency
	Fibrinogen	Fibrinogen deficiency
	Blood or plasma	Any hemorrhagic disorder
Ancillary agents	Anticoagulants	Polycythemia, thrombocythemia
	Antibiotics	Agranulocytosis, bone marrow failure, leukemia

hydrate complex (Astrafer) can be accepted Ed]

OTHER METALS —At this point, it should be stated that we find no indicatio for the administration of other metals such as *copper, manganese, cobalt,* or molyb denum in the therapy of anemia It is true that cobalt in the form of cobaltou chloride is capable of eliciting a mild erythropoietic response which may be helpfu occasionally in the anemia of uremia or chronic infections But the erythropoieti response appears unphysiologic in that it continues only so long as the cobalt i administered and side effects of gastrointestinal and thyroid disturbances occur ring with cobalt administration seem to militate against its use

Vitamin B_{12} in Pernicious Anemia —With the firm establishment in recen years of vitamin B_{12} as the active antianemia principle in liver extract, there ap pears to be very little indication for the latter as a therapeutic agent This con clusion seems justified in spite of the many liver injections" that patients continue to receive However, liver extract may be used as a source of vitamin B_{12} in place of more concentrated preparations, since liver extract is now assayed according to its content of the vitamin Another use according to scattered reports, may be in certain rare types of chronic anemia which are said to respond only to crude liver injections However in general, liver preparations have nothing to recom mend their use over the readily available vitamin B_{12} preparations

INITIAL THERAPY —The initial therapy of a 'fresh" case of pernicious anemia or one in relapse is quite flexible within certain bounds As little as 1 mcg in tramuscularly daily can produce complete remission in certain cases However this represents minimum therapy where one is usually interested in replacing de pleted B_{12} stores The other extreme is represented by the demonstration that, as 80 mcg per dose is exceeded, proportionally larger quantities are excreted in the urine Therefore, we adopt a middle road and may administer 30 to 100 mcg vitamin B_{12} intramuscularly daily for 5 to 7 days, then every other day for the second week and at progressively longer intervals thereafter Finally, the patient is maintained on approximately 2 mcg daily, which we usually give in a single monthly intramuscular injection of 60 mcg

MAINTENANCE —The exact maintenance dosage and interval of administra tion varies with each case according to tendency to relapse, particularly neurologi cal relapse Patients should be tested for vibratory sense and tendon reflexes at the time of each visit When neurological involvement is apparent, supermaximum doses of vitamin B_{12} are justified for initial and maintenance therapy

Oral Therapy Recently there have been many investigations into the feasi bility of maintaining the patient with pernicious anemia on oral therapy This consists of daily administration of tablets or capsules containing vitamin B_{12} in conjunction with stomach extract, thereby supplying intrinsic factor' and permit ting absorption of the vitamin This method of maintenance therapy has proved satisfactory and is no doubt preferred by many patients However, at present, B_{12} given by injection appears more dependable and it is cheaper Furthermore, it requires that the patient be observed from time to time Patients maintained on pills alone often forget to return to their physician It may prove advantageous in certain cases to provide optimum therapy or to prolong the interval between injections by combining both the oral and injectable forms of therapy

in meats, eggs, cheese, milk, and other foods, and is synthesized by intestinal bacteria It is readily absorbed from the gastrointestinal tract in the presence of "intrinsic factor," is found in plasma in combination with α globulins mainly, and is stored for the most part in the liver The exact mechanism through which vitamin B_{12} functions as an antianemia principle is uncertain However, it is known to be concerned in the formation of nucleic acids and is closely related in its action to the action of folic acid There are no known acute or chronic toxic reactions to the administration of vitamin B_{12} even in large doses parenterally

Other members of the B vitamins including pyridoxine, riboflavin, and nicotinic acid, undoubtedly function in hematopoiesis, but they are relatively unimportant from a therapeutic standpoint and therefore will be omitted from this discussion Vitamin C appears to be interrelated in the functions of vitamin B_{12} and folic acid without having a specific action of its own in hematopoiesis

Folic Acid —Folic acid or pteroylglutamic acid is a yellow crystalline compound whose chemical structure consists of a pteridyl group, p-aminobenzoic acid and glutamic acid A number of conjugate forms are known, and the formyl derivative, so called citrovorum factor or folinic acid, is worthy of mention These substances are widely distributed in nature and maximally concentrated in certain foods such as liver, yeast, and green leafy vegetables They are also synthesized by intestinal bacteria so that minimal daily requirements are difficult to determine Absorption from the gastrointestinal tract is efficient except in cases with severe malabsorptive defects As indicated previously folic acid plays a role with vitamin B_{12} in the synthesis of nucleic acids But the two cannot be substituted interchangeably, as evidenced by the fact that folic acid may produce a hematologic remission in pernicious anemia while the neurologic lesions progress

Radio-Phosphate —Radioactive phosphorus (P^{32}) inhibits bone marrow activity by its emission of beta rays, which have a maximum penetration in tissues of about 0 7 cm This isotope has a physical half-life of 14 3 days, but since it is metabolized and excreted as any stable phosphorus atom, it has an estimated biologic half-life in man of 8 days Phosphorus is incorporated in the nucleoproteins of growing cells, which accounts for the localization and effectiveness of the radioactive isomer in proliferating tissue such as marrow or neoplasms Overdosage may cause severe bone marrow despression or fatal aplasia

Vitamin K —Vitamin K exists in a number of forms, all of which contain a naphthoquinone group It occurs naturally as vitamin K_1 in plants and vitamin K_2 in animals However, the dietary source is relatively unimportant as the vitamin is synthesized by intestinal bacteria and, being fat soluble, is readily absorbed in the presence of bile salts The vitamin is essential for the synthesis of normal amounts of prothrombin by the liver, although the details of this process are unknown Obviously, prothrombin production may be impaired through hepatic dysfunction or through deficient supply of vitamin K secondary to obstructive biliary disease, absorptive defects, or disruption of bacterial synthesis as a result of antibiotic therapy There is evidence that excessive administration of vitamin K in man may cause prolongation of the prothrombin time, particularly in the presence of hepatic dysfunction Also, hyperbilirubinemia has been noted in premature infants following excessively high doses of vitamin K

Table 43 Summary of Therapy of Hypoplastic Anemia or Bone Marrow Failure

First Step		
	1 Transfusions	Whole, fresh blood in an effort to maintain approximately 8 Gm of hemoglobin Fresh [illegible]
	2 Corticosteroids	[illegible] thorough trial
	3 Antibiotics	Tetracycline, 1 Gm daily, or other antibiotic as indicated if infection imminent due to low granulocyte level
Second Step		
	1 Splenectomy	To be considered as a final measure and more likely to be effective when there is evidence of hematopoiesis in the marrow
	2 Thymectomy	In rare cases in which a thymus tumor is detected

Corticosteroids in Hypoplastic Anemia or Bone Marrow Failure—The use of corticosteroids in this group of diseases is a moot point since, as pointed out previously, the exact effect of steroids on the bone marrow is unknown Our feeling is that these cases should be treated thoroughly, including the use of corticosteroids, because remissions do occur Fresh blood, collected in plastic bags or siliconized glassware, should be administered as necessary to maintain the hemoglobin at an approximate level of 8 to 9 Gm There is no necessity for pushing blood values higher as patients become "conditioned" to these relatively low values of hemoglobin and, furthermore, too many transfusions may have a suppressive effect on erythropoiesis Antibiotics may be administered in the presence of extremely low granulocyte counts as a prophylactic measure For this purpose, one of the broad-spectrum antibiotics such as tetracycline in doses of 1 Gm daily orally is satisfactory

In our experience, corticosteroids seem beneficial and appear to have produced remissions in rare cases In any event, they tend to reduce the bleeding tendency, possibly through a nonspecific effect on vascular integrity In cases where there may be an element of hemolysis, corticosteroid therapy is pre eminent In short, we give corticosteroids a thorough trial in any case of hypoplastic anemia, beginning with large doses of prednisone (100 mg daily) for 7 to 10 days and then gradually reducing the dosage, depending on any obvious effect on the blood count until a relatively safe maintenance dosage is attained (5 to 20 mg prednisone) If prednisone therapy appears ineffectual after a thorough trial, we may try large doses of ACTH or cortisone on the basis that one corticosteroid may be effective where another is not As a final measure, splenectomy may be advisable since it has proved beneficial in a few cases particularly those with some evidence of hematopoiesis in the marrow The possibility of transplanting normal marrow is now under investigation (Table 43)

Corticosteroids in Autoimmune Hemolytic Anemia—The corticosteroids and prednisone in particular, have proved in our hands very valuable in the management of autoimmune hemolytic anemia of either the "idiopathic" or the "symptomatic" type In this disease, our program of therapy involves four distinct phases (1) initial treatment with high doses of corticosteroids until a remission has been ob

Although the main applications of vitamin B_{12} are in pernicious anemia and postgastrectomy anemia, in which the source of intrinsic factor may have been removed, there are a number of cases of macrocytic anemia which etiologically would be classified as responsive to folic acid and yet do not respond to folic acid In these cases, after a thorough trial of folic acid, B_{12} should be administered and may induce a remission (Table 42)

Table 42 Summary of Therapy of Pernicious Anemia

Initial and relapse therapy	First week	Vitamin B_{12} 30 to 100 mcg I M daily—dosage depending on individual case
	Second week	*Vitamin B_{12} 30 to 100 mcg I M every 2 days*
	Third to sixth week	Vitamin B_{12} 30 to 100 mcg I M weekly
Maintenance therapy		Vitamin B_{12} 60 to 100 mcg I M monthly—dosage and interval depending on individual case

Folic Acid in Macrocytic Anemias —The exact interrelationship between vitamin B_{12} and folic acid in hematopoiesis is unknown Either will cause a hematologic remission in pernicious anemia but if folic acid is the sole therapeutic agent in this disease, the neurologic manifestations may progress in spite of the improved blood picture For this reason, folic acid is contraindicated as the primary or sole therapeutic agent in pernicious anemia

In spite of the fact that the exact metabolic roles of vitamin B_{12} and folic acid remain an enigma by the use of newer diagnostic methods utilizing vitamin B_{12} serum levels radioactive cobalt labeled vitamin B_{12} uptake studies and various tolerance tests designed to demonstrate absorption defects, it is possible to delineate the specific deficiency in most cases of macrocytic anemia In general however, given a case of macrocytic anemia, which according to the clinical picture is not pernicious anemia or intrinsic factor deficiency as a result of gastrectomy, the first therapeutic agent of choice is folic acid Examples of such macrocytic anemias have already been enumerated and include sprue, steatorrhea, celiac disease macrocytic anemia of pregnancy, and surgical or developmental anomalies of the gastrointestinal tract, and fish tapeworm infestation In these conditions, folic acid may be administered initially in doses from 10 to 100 mg orally daily with subsequent maintenance doses of 5 to 10 mg daily

In some of these conditions, particularly the malabsorption group, hematologic remission may not be complete, but clinical improvement may be sufficient to warrant continuation of therapy with folic acid Where there is no response to folic acid and where facilities for detailed absorptive studies are not available, vitamin B_{12} may be administered parenterally, with response in some cases

Citrovorum Factor —Citrovorum factor appears to have the same action as folic acid although there are reports of cases of macrocytic anemia which failed to respond to folic acid but which responded when citrovorum factor was administered However, citrovorum factor is specific in combating the toxic effects of antifolic compounds such as Aminopterin, in which instance folic acid may be ineffective Citrovorum factor may be administered intramuscularly in doses of 3 to 6 mg, once or twice daily

with a broad spectrum agent such as tetracycline 1 Gm orally daily or other antibiotics as indicated by sensitivity studies if specific organisms can be cultured In most cases, infection can be controlled and granulocytes reappear in the bone marrow and peripheral blood without other forms of therapy

However, there are cases in which the course is more protracted, and in these one may *administer corticosteroids on the basis that they may suppress antibody formation and may even have a myelostimulatory effect* Suffice it to say that, in our own series of cases, we have rarely resorted to steroid therapy, and *in these it is* impossible to assess the role of the steroid

Corticosteroids in Idiopathic Thrombocytopenic Purpura—In 1916, Kaznelson demonstrated that splenectomy was an effective therapeutic procedure in idiopathic thrombocytopenic purpura since, postoperatively, there is a fairly consistent rise *in platelet levels* Thereafter for years, splenectomy remained the treatment of choice, and the operation was frequently an emergency procedure, often attended by a high mortality rate

Then, about 1950, two measures of great importance were added to the therapeutic regimen of idiopathic thrombocytopenic purpura It was found that ACTH or cortisone could effectively control the hemorrhagic state prior to splenectomy, thereby rendering the patient a better operative risk Also, by collecting blood in plastic bags or siliconized glassware, it became possible to raise the patient s platelet count significantly by transfusing fresh blood containing viable platelets *But as more splenectomies were done and patients were followed for longer periods,* it became apparent that there was a high relapse rate in spite of months or even years of remission

Originally, the action of ACTH and cortisone in controlling the hemorrhagic diathesis was felt to be a nonspecific effect on vascular continuity since increased platelet counts were not prominent However, the corticosteroid role was reinvestigated due to the frequent relapses following splenectomy, and it became apparent *that most cases respond to corticosteroid therapy with a rise in platelets,* possibly as a result of suppression of antibodies This response has been so consistent, particularly with prednisone in our laboratory, that we feel corticosteroids have largely replaced splenectomy in the therapy of idiopathic thrombocytopenic purpura In a recent review of 17 consecutive cases of this disorder treated by us, only 6 cases failed to respond to prednisone alone, and 4 of these failures subsequently responded to splenectomy and prednisone

We customarily classify cases of idiopathic thrombocytopenic purpura as acute or chronic, depending on the history, although admittedly this division is sometimes possible only in retrospect Our initial daily dose of prednisone may vary from 50 to 250 mg, depending on the condition of the patient and the urgency of the situation On this dosage, hemorrhagic manifestations usually cease, and in most cases the platelet count begins to rise within 14 days *The platelet count is* usually normal in 8 to 30 days, acute cases tending to respond faster than chronic ones *As the platelet count rises toward normal,* the dose of prednisone is reduced, with an aim toward maintaining a normal or slightly subnormal platelet count with the patient on less than 10 mg prednisone daily In some cases, particularly acute ones, it is possible to discontinue prednisone entirely A return to a com

Table 44 Summary of [illegible]

Initial Therapy	
	1. Prednisone [illegible]
	2. Transfusions [illegible]
Maintenance Therapy	
	1. Gradual [illegible]
	2. Discontinue [illegible]
Therapy of Relapse	
	1. Same as [illegible]
	2. Splenectomy [illegible]

tained (2) reduction [illegible] as long as the remission is sustained (3) reinstitution of [illegible] maintenance therapy [illegible] clinical remission, and (4) final appraisal as to whether the hemolytic process can be controlled on doses of steroid which do not [illegible] whether splenectomy must be instituted.

In autoimmune hemolytic anemia there is no standard initial dose of steroid. We know from experience that there is a "minimum dose" for most cases, and therefore it is better to start with a very large dose and then reduce it. We now use prednisone almost exclusively, and the initial daily dosage varies from 50 to 100 mg. Beginning remissions are heralded by a reduction in reticulocytes, a maintenance of the red cell count, a reduction in icterus and bilirubinemia, and an improvement in the clinical status of the patient. Following the initial beneficial response, the dose of prednisone is gradually reduced to the smallest amount which will sustain satisfactory hemoglobin and erythrocyte values. Impending relapse is indicated by a slight fall in the red cell count or hemoglobin together with a rising reticulocyte count. The Coombs test may remain positive even though other manifestations of hemolytic disease are absent. Cases which respond only partially to corticosteroid therapy or which for control require doses of corticosteroids that produce toxic side effects are then considered for splenectomy. Relapses following splenectomy are uncommon, but when they occur they are managed similarly with steroids.

The over all picture of results with corticosteroids or corticosteroids plus splenectomy indicates a complete remission rate of approximately 80 per cent. In this regard several points should be realized. Individualization in the management of each patient is the keystone of therapy. Although we present representative dosages in a discussion such as this, patients vary widely in their responsiveness. Once an autoimmune mechanism develops, it is usually self-perpetuating and may persist permanently or may relapse after years of remission. Therefore, management varies greatly from one case to another (Table 44).

Antibiotics in Agranulocytosis.—There is increasing evidence that agranulocytosis is an immune disorder resulting from an antigen-antibody reaction affecting granulocytes, and that if an offending drug or other toxic substance can be detected and removed, the granulocytes will recover spontaneously. This was seldom possible before the era of antibiotics; the patient usually died of overwhelming infection as a result of granulocytopenia. At present, however, we use routine therapy

By vascular pseudohemophilia we refer to the hemorrhagic disorder in which prolonged bleeding time is the only demonstrable abnormality Therefore, we include cases in which thrombasthenia is detectable (von Willebrand's disease) as well as those in which an unknown vascular defect is responsible for symptoms Either of these appears to respond favorably to corticosteroid therapy as outlined above for anaphylactoid purpura, and here again we use the corticosteroids for a brief period when symptoms are present The manner in which corticosteroids are beneficial in these cases is unknown There seems to be a specific action in restoring vascular integrity as is evident in thrombocytopenic purpura where hemorrhagic manifestations may cease as a result of corticosteroid therapy long before there is evidence of a rise in platelets

Therapy in Polycythemia Vera—There are two main methods of controlling the high blood levels of polycythemia vera (1) removal of the excess blood by repeated venesections, and (2) reduction of the activity of the bone marrow by use of myelodepressant agents such as P^{32} or Myleran, and perhaps by institution of *iron deficient diet*

VENESECTION —Venesection alone had been the mainstay of therapy in polycythemia for many years However, with the advent of radioisotopes and the demonstration that P^{32} is concentrated in the marrow with destruction of its cellular elements this substance became the preferred method of therapy by many workers

RADIO PHOSPHATE —P^{32} may be administered orally in water or intravenously,

if the red cell count and, particularly, the platelet count remain at dangerously high levels

Combinations With Venesection In most cases, venesections are combined with P^{32} therapy That is a 'new' case or one in relapse is given the estimated dose of P^{32} and at the same time venesections are started daily or every other day The first few attempts at venesection are usually difficult because of the increased viscosity, therefore, one must be satisfied with small amounts of blood and repeat the procedure daily or every other day, gradually increasing the quantity withdrawn at each operation until the hematocrit is finally below 50 per cent or the hemoglobin below 14 Gm The hematocrit and platelet levels in 2 to 3 months are then used as criteria of the effectiveness of the previously administered P^{3}

Dangers There is no doubt that the use of P^{32} in polycythemia vera has been very effective in producing remissions and rendering these patients symptom free for intervals of 1 to 2 years in some cases However, we would be remiss were we not to mention that at present there are statistics to suggest that there is a higher incidence of leukemia as a terminal development in patients with polycythemia vera treated with P^{32}, than in those previously treated with venesections alone The subject is far from settled at this time because of the lack of controlled series Suffice it to say that because of the incidence of leukemia in P^{32} treated cases we are again treating most of our cases with venesections

Table 45 Summary of Therapy of Idiopathic Thrombocytopenic Purpura

Initial Therapy	1 Prednisone 50 to 250 mg daily until platelet count begins to rise 2 Transfusions of fresh, whole blood collected in plastic bags or siliconized bottles for platelet effect, the number depending on the degree of hemorrhage
Maintenance Therapy	1 [illegible] 2 [illegible]
Therapy of Relapse	1 Same as remission therapy 2 Splenectomy if doses of prednisone required to maintain a remission are toxic or too high to be compatible with prolonged therapy

pletely normal level of platelets is not essential, since the patient can get along well on approximately one half normal platelet count without evidence of bleeding tendency

However, in some cases the platelet count may fall to pretreatment levels when the prednisone is reduced or discontinued When this happens, the high dosage of prednisone is reinstituted, usually with the same beneficial effect as the first course Then again we attempt to reduce the prednisone without a relapse in the platelet count In other words, we try to render the patient symptom free with normal or subnormal platelet levels on a daily prednisone dose of less than 10 mg Where this is impossible, we resort to splenectomy, but only after a thorough trial of prednisone We have come to regard 'medical therapy" the treatment of choice in idiopathic thrombocytopenic purpura, resorting to splenectomy only as a last measure (Table 45)

Corticosteroids in Vascular Purpuras.—As mentioned previously, the majority of purpuras which occur on the basis of a vascular defect are benign and do not require therapy The two most important from the standpoint of frequency of occurrence and morbidity are anaphylactoid or Henoch Schönlein purpura and so called "vascular pseudohemophilia "

Henoch Schönlein purpura may be acute or chronically recurrent with generalized involvement of the skin, joints, gastrointestinal tract, and kidneys due to a widespread vasculitis affecting small blood vessels Some cases are mild and of short duration, requiring little more than salicylates and sedation for relief of symptoms In the more severe and particularly in recurrent attacks, we administer corticosteroids with prompt relief of symptoms in most cases Our rationale for the use of corticosteroids is that anaphylactoid purpura appears to be an autoimmune disease involving small blood vessels throughout the entire body Therefore, corticosteroids would be expected to exert a beneficial effect, as in most allergic disorders We ordinarily administer corticosteroids for 1 to 2 weeks during the acute attack We may start with 50 mg of prednisone daily for 2 to 3 days and then rapidly reduce the dose over the next few days, depending on the progress of the patient Proportionally smaller doses are used for children We do not use corticosteroids prophylactically except in rare cases where there are frequent recurrences at short intervals In this case we may maintain the patient on 5 to 10 mg prednisone daily

Table 47 Summary of Therapy of Hemophilia

Hemorrhagic Phase	
	1 Fresh whole blood or fresh frozen plasma continuously until hemorrhage stops
	2 If open wound, debridement followed by pressure dressings of thromboplastin or thrombin
	3 After hemorrhage ceases continue to administer fresh whole blood or fresh frozen plasma approximately 2 0 ml per kilogram every 4 to 8 hours for several days or more
Nonhemorrhagic Phase	
	1 Education of patient and family
	2 Orthopedic measures to limit deformities from hemarthroses
Prophylactic Therapy	
	1 [illegible]
	2 [illegible] on the operation and progress

Prophylactic AHG Administration —AHG may be administered prophylactically in instances where dental extractions are mandatory In such cases we prefer to hospitalize the patient and give 250 to 500 ml plasma just prior to operation with continuous plasma infusion during the operation Postoperatively plasma is administered every 4 to 8 hours in amounts of approximately 2 ml per kilogram for several days, depending on the patient's progress

Prophylactic AHG may also be necessary in preparation for abdominal surgery, particularly appendectomy However, hemophiliacs are notoriously poor surgical risks, and therapy should always lean toward conservatism Indeed, most "surgical abdomens" in hemophiliacs represent occult bleeding, and the mortality rate is compounded by surgery (Table 47)

Vitamin K in Prothrombin Deficiency—Prothrombin deficiencies may be congenital or acquired Fortunately, the congenital varieties are quite rare and, since they do not respond to the administration of vitamin K, they must be treated during hemorrhagic episodes by the administration of whole blood or plasma

Acquired Hypoprothrombinemia —Acquired hypoprothrombinemia may occur neonatally as so called hemorrhagic disease of the newborn or as the result of biliary disease, malabsorption, antibiotic sterilization of the bowel, or anticoagulant therapy In any of these situations, vitamin K may be administered orally or parenterally, depending upon details of the particular case and urgency of the situation However, in general we administer vitamin K parenterally, using either menadione or vitamin K_1 The former, given in a dose of 2 mg subcutaneously, will usually result in greater than 20 per cent improvement in the prothrombin time (Quick) in 12 hours in the presence of normal liver function And this method of therapy appears to be satisfactory for most cases of hypoprothrombinemia except those resulting from anticoagulant therapy In these, as perhaps in all hypoprothrombinemias responding to vitamin K therapy, vitamin K_1 appears to be of greater efficacy in restoring prothrombin than the synthetic preparations Vitamin K_1 may be administered orally in doses of 5 to 20 mg daily or intravenously in 5 per cent glucose solution in doses of 5 to 50 mg or more daily The amount of vitamin K_1 required varies with each case, and it must be administered until the prothrombin

Table 46 Summary of Therapy of Polycythemia Vera

Initial Therapy	1	[illegible]
	2	[illegible]
	3	[illegible]
Maintenance Therapy	1	Repeat P^{32} in dose of 1 to 4 millicuries in 2 to 3 months if blood levels still too high
	2	In case of Myleran titrate dosage according to response
Relapse Therapy		Same as initial therapy

MYLERAN —We are utilizing busulfan (Myleran) in small doses for suppression of hematopoiesis instead of P^{32} As yet it is too early to draw any definite conclusions but Myleran seems to be as effective in limiting hematopoiesis as P^{32}, it is readily available, and the dosage is easier to titrate (Table 46)

Antihemophilic Globulin in Hemophilia —Therapy in the hemophiliac varies according to whether he is bleeding, asymptomatic, or contemplating surgical procedures Therefore, we shall discuss therapy in the hemorrhagic episode, the nonhemorrhagic phase, and as a prophylactic measure

HEMORRHAGIC EPISODE —It has been established that the hemophiliac who is actively bleeding, as in spontaneous hemarthrosis, probably has an antihemophilic globulin (AHG) level of less than 5 per cent of a mean normal' and that hemorrhage will probably cease in most cases when this level is raised to 5 to 20 per cent Therefore, AHG is administered either in the form of fresh whole blood, if there is anemia, or plasma, either fresh fresh frozen, or lyophilized, or as concentrated Fraction I of Cohn The use of Cohn s Fraction I has been largely abandoned by us because individual fractions frequently lack potency and because it is in this fraction that the virus of hepatitis tends to be concentrated At present, potent AHG extracts from animals are being investigated and may prove practical

In general, then, for the hemophiliac who is actively bleeding, we administer fresh blood or plasma continuously until hemorrhage has apparently ceased and then approximately 2 ml per kilogram every 4 to 8 hours for several days, depending on the circumstances of the case and the progress The initial amount of blood or plasma required to stop hemorrhage may vary from 1 pint in a mild case to 150 pints in a severe case where a so called "anticoagulant" has developed against AHG In some instances of the latter complication no amount of blood is effective

If hemorrhage is external, as following a dental extraction or a traumatic wound, in addition to the administration of AHG, topical thrombin and even thromboplastin may be useful locally in a pressure dressing These are applied directly to the bleeding surface after débridement

NONHEMORRHAGIC PHASE —It is the general consensus that the administration of AHG in the absence of hemorrhage is useless It has been demonstrated that parenterally administered AHG remains in the system for only 4 to 6 hours, indicating the improbability of any prolonged benefit

The most important measures during this phase are education of the patient toward prevention of trauma and institution of any necessary orthopedic procedures in an attempt to prevent deformities from hemarthroses

normal ones A step in this direction has already been made by introduction of the alkylating agents, and research continues in an effort to make their action more selective Also, knowledge of an etiologic agent such as a virus in neoplastic growths may lead to the development of prophylactic methods Any or all of these may be future therapeutic possibilities as a result of further insight into normal and abnormal marrow physiology

SELECTED REFERENCES

Dameshek W, and Komninos, Z D The Present Status of Treatment of Hemolytic Anemia With ACTH and Cortisone, Blood 11 648, 1956

Dameshek, W, Rubio, F, Jr, Mahoney J P, Reeves, W H, and Burgin, L The Treatment of Idiopathic Thrombocytopenic Purpura With Prednisone, J A M A 166 1805, 1958

Franklin, M, Rohse, W G, de la Huerga, J, and Kemp, C R Chelate Iron Therapy, J A M A 166 1685, 1958

Fruhman, G J, and Gordon, A S Quantitative Effects of Corticosterone on Rat Bone [illegible] 88 130, 1955

Granick [illegible]

Hechter, [illegible] Action [illegible]

Quittner, [illegible] Doses of [illegible] 6 513 [illegible] 1951

L[illegible] H C C[illegible] Stat[illegible] of Therap[illegible] Anem[illegible] J A M A 167 735 1958

F[illegible]

S[illegible] Stratton Inc

Stoerk, H C Cortisone in Relation to Lymphoid Tissue and Immunity In Fifth Annual Report on Stress 1955 56, by H Selye and G Heuser, New York, M D Publications, Inc

Sturgeon, P Iron Metabolism—a Review With Special Consideration of Iron Requirements During Normal Infancy Pediatrics 18 267, 1956

Wintrobe M M Clinical Hematology, ed 45, Philadelphia, 1956, Lea & Febiger

is restored to the desired level When restoration of normal prothrombin activity represents an emergency, whole blood or plasma should be utilized as a source of available prothrombin in addition to the administration of vitamin K

Fibrinogen in Hypofibrinogenemia —Hypofibrinogenemia or afibrinogenemia may occur as congenital deficiencies, in which cases there are not usually serious hemorrhagic manifestations This is fortunate because efforts to raise the fibrinogen level by administration of fibrinogen are successful only temporarily, the administered fibrinogen disappearing in 3 to 4 days

More commonly, hypofibrinogen occurs as a complication of obstetrical conditions, including abruptio placentae, long standing intrauterine fetal death, and amniotic fluid embolization It has also occurred as a complication of prostatic, lung pancreatic, and uterine surgery, as well as in certain malignancies In some cases, the hypofibrinogenemia is the result of a fibrinolytic mechanism In any case, recognition of hypofibrinogenemia depends mainly on a clinical awareness on the part of physicians engaged in the fields where the condition most commonly occurs

Fortunately, a simple test (Fibrindex) which demonstrates failure of the patient s plasma to form a normal clot on addition to thrombin is readily available and serves as a rough index of fibrinogen level Where suitable laboratory facilities are available, however, actual fibrinogen determinations can be made

Once the diagnosis of hypofibrinogenemia has been established therapy becomes an emergency since these patients rapidly develop circulatory collapse Whole blood either fresh or stored or plasma is administered as soon as possible and serves as a source of fibrinogen as well as replacement of blood volume In addition concentrated fibrinogen is administered intravenously, usually 2 to 10 Gm in divided dosage depending on progress of the patient After cessation of hemorrhage, approximate fibrinogen levels may be determined at intervals for several days to be certain that adequate fibrinogen is maintained

RATIONAL BASIS FOR NEW DRUGS IN HEMATOLOGY

A number of *specific* therapeutic agents presently available in hematology are on a sound physiologic basis, i e , each agent supplies the missing factor and its use is curative Examples of such agents are iron in iron deficiency anemia, B_{12} in pernicious anemia, folic acid in most macrocytic anemias, vitamin K in most hypoprothrombinemias, and fibrinogen in hypofibrinogenemia Obviously anyone's hope for the future would be that factors as specific and physiologic as these could be discovered for such serious diseases as leukemia, lymphoma, aplastic anemia, idiopathic thrombocytopenic purpura, and others

We can hope for factors capable of controlling bone marrow production as a thermostat controls a furnace These would include factors capable of stimulating or suppressing normal growth, differentiation, maturation, and exfoliation of marrow cells These factors may even be specific for a cell line like the erythropoietic factor which is already being investigated widely Then if abnormal growth and maturation are found to be uninfluenced by normal control mechanisms, one would desire agents capable of destroying the abnormal cells preferentially and sparing

nosis and proper treatment warrant the use of the drugs Then therapy with drugs is based on a reasonable understanding of how they produce their effect how the degree of effect can be controlled so that untoward effects are avoided successfully as possible

Fortunately the physician need not be conversant with the many details wh are now involved in the present day concept of the mechanisms concerned in coagulation of blood No other field of physiology is more rampant with ter nology which is sometimes confusing even to those persons who are actively c ducting research in this field This confusion in terminology results from the co plexity and the only partially evaluated, multiple details of the clotting mechani For general purposes, the formation and resolution of the clot result from following sequence of reactions

1 Formation of thromboplastin
2 Conversion of prothrombin to thrombin by thromboplastin
3 Conversion of fibrinogen to fibrin by thrombin
4 Resolution of fibrin by fibrinolysin

Although tissue thromboplastin is liberated whenever the integrity of the tiss cells is disrupted, this form of thromboplastin is usually involved in the clotting blood only when the tissue is grossly traumatized However, it may be that clotting in the intact vasculature is initiated by this form of thromboplastin resu ing from a minor amount of tissue injury or pathology, for it is well recogniz that blood does not spontaneously clot in the normal intact vasculature

In order for the rapid formation of thromboplastin to take place, the blo must contain a normal complement of platelets, antihemophilic globulin, a plasma thromboplastin component Although the source of blood thromboplast is not clearly established it is believed to be derived either from the platelets the antihemophilic globulin When thromboplastin becomes available it will rea with prothrombin resulting in the formation of thrombin However, rapid form tion of thrombin involves at least two additional protein factors which are normal present in plasma These factors are known as convertin and accelerin Conve tin is involved in the initiation of the conversion of prothrombin to thrombin an accelerin accelerates the rate of this reaction Calcium ions also take part in th reaction, but clinically, calcium ions are not a limiting factor In the presence o thrombin, fibrinogen is rapidly converted to fibrin Fibrin is the matrix of the clo Normal blood also contains the precursor (profibrinolysin) of an enzyme (fibrino lysin) which is capable of resolving the fibrin of a clot All therapeutic agent which influence the coagulation or resolution of blood produce their effect throug influencing one or more of the reactions mentioned above

THE ANTICOAGULANTS

Anticoagulant therapy represents an attempt to prevent enlargement of ar existing thrombus and the occurrence of additional new thrombi in the vascular bed Anticoagulant therapy is used for this purpose in the treatment of the clinica conditions which follow

THE CHOICE OF DRUGS AFFECTING THE COAGULATION OF BLOOD

T A Loomis, Ph D, M D

INTRODUCTION

Drugs which influence the coagulation of blood may be divided into four main groups on the basis of their clinical usefulness The first group is the anticoagulants and includes those agents which are given for the purpose of preventing the clotting of blood in the intact vasculature of the patient The second group consists of the coagulant agents which may be given for the purpose of correcting certain hemorrhagic tendencies but which are not intended to produce actual clot formation The third group consists of the coagulant agents which are intended to arrest bleeding or promote coagulation of blood by the actual production of a clot at the site of their application The fourth group consists of those lytic agents which are given for the purpose of enhancing resolution of a blood clot This chapter will consider these four groups of drugs in the order presented above In the instances in which a single drug may be useful in more than one category, reference will be made to its additional uses in the discussion of each category

Any preference for the recommendation of a particular agent when several similarly used agents are available is based on the following considerations The first consideration will be the nearness to which the drug approaches all of the criteria which are considered as being ideal for the hypothetically perfect drug The second consideration will be the degree to which the drug has proved itself by the test of time and use in the hands of many investigators The last consideration is rather intangible one as it is concerned with the individual physician's preference hich has resulted from personal experience in using the drugs Unfortunately rsonal experience is not usually scientifically controlled and therefore is not sub ct to experimental evaluation However, such personal experience frequently phasizes merits and drawbacks associated with the use of particular drugs

Therapy with any drug which influences the coagulation of blood is based on roper accurate diagnosis and a sound understanding of the fundamental con ts of the mechanism involved in the coagulation of blood and resolution of blood

Many of the drugs which are considered in this chapter are potentially ful agents A patient should not be subjected to such agents unless the diag

and the more slowly acting, synthetic coumarin and coumarin like compounds The closest approach to ideal anticoagulant therapy is accomplished through the combined use of heparin and Dicumarol or an agent like it Recent evidence indicates that the coumarin like compound which most closely approaches the prerequisite of the ideal agent is warfarin sodium, but this compound is the newest of the coumarin like compounds and has not yet had the test of time and use in the hands of numerous investigators Where there is no necessity for rapid initiation of anticoagulant therapy, Dicumarol or warfarin is the drug of choice

Heparin.—Heparin is a mucoitin polysaccharide which is normally present in blood and which some investigators believe is the naturally occurring agent which maintains normal fluidity of the blood The presently available forms of heparin are completely nontoxic except for their anticoagulant action Its advantages are that its anticoagulant action on the blood is immediate, its effect can be determined by the relatively simple Lee White clotting time test at the bedside, a single intravenous dose produces a predictable uniform response, it does not produce cumulative toxic effects on repeated administration, and its duration of action is sufficiently short so that if bleeding occurs treatment of overdose usually involves only discontinuance of the drug

The greatest disadvantage in heparin therapy is that the drug must be administered by the parenteral route The intravenous route is the route of choice because subcutaneous or intramuscular preparations are prone to produce either pain at the injection site or hematoma formation on repeated administration and an unpredictable degree of effect on the coagulation of the blood in different patients Another disadvantage of heparin is its extremely short duration of action The short duration of action (2 to 6 hours depending on the dose) following intravenous administration of heparin results in a nonstable degree of effect However stable uniform intensity of effect on the clotting time can be obtained by continuous intravenous infusion of heparin Continued medication with heparin is costly not only because of the initial high cost of the drug but also because of the necessity for hospitalization during medication arising from the need for repeated injections at 4 to 6 hour intervals

Heparin has four effects on the blood clotting mechanism First, it has an antithromboplastin action which is mediated through a plasma cofactor, that is, heparin reacts with a plasma cofactor, resulting in the formation of a substance which inactivates thromboplastin Second, heparin has an antithrombin action which is also mediated through a normal plasma factor, that is, it is believed that heparin either reacts with a plasma cofactor or activates the precursor of an antithrombin which results in the formation of a substance which inactivates thrombin Third, heparin decreases the adhesiveness of the platelets Although the role of the platelets in the clotting mechanism is not clearly defined, it is believed by some investigators that initiation of the clotting process is associated with the fusion and agglutination of the platelets Last, heparin has been shown in animal experiments to promote the resolution of a newly formed clot However, heparin does not dissolve the fibrin of a well established blood clot

Dosage.—Adequate heparin induced anticoagulant therapy is present when the clotting time is elevated from 2 to 3 times normal value as measured by the

1 Pulmonary embolism due to an intravascular clot
2 Coronary occlusion with myocardial infarction
3 Venous or arterial thrombosis
4 Postoperatively and post partum in all patients who have a previous history of embolic disease, and following all major vascular surgery
5 Rheumatic heart disease with auricular fibrillation
6 Excessive traumatic injury, gangrene, or frostbite of the extremities

Although the currently available evidence is inconclusive, apparently favorable results can be expected by the use of anticoagulant therapy in chronic obliterative vascular disease and in congenital heart failure (for the prevention of thrombosis)

Although there is only meager evidence to indicate that the anticoagulant drugs are capable of hastening resolution of preformed clots, these drugs should be administered to prevent extension of the initial clot Unless the initial thrombus is of such magnitude as to occlude the blood supply to a vital structure or area, adequate anticoagulant therapy will prevent extension of the clot and the occurrence of additional thromboembolic sequelae

The nature of the diseases which indicate the use of the anticoagulant drugs frequently necessitates the prolonged use of these agents Adequate prolonged therapy can be achieved only when the physician has available adequate facilities for determining certain coagulation tests Excessive drug effect may lead to hemorrhagic complications, and inadequate dosage will not achieve protection for the patient from the thromboembolic complications for which he is being given the drugs Therefore, it is necessary for the physician to acquaint himself with the laboratory tests which are used to evaluate the degree of anticoagulant effect and also for him to impress upon the patient the importance of adhering to the suggested dosage regimen

The Ideal Anticoagulant—The theoretically ideal anticoagulant agent should have all of the following features It should have a reasonably high therapeutic index, and the therapeutic dose should be uniform between individuals and not produce an effect of such magnitude so that excessive therapeutic effect (toxic effect) will occur in any single patient The therapeutic dose should produce a predictable response on the coagulation mechanism which can be measured by a simple laboratory test It should be effective when administered by either the oral or parenteral route It should have a rapid onset of action for use in medical emergencies and a sufficiently prolonged duration of action so that continuous medication can be accomplished with little inconvenience to the patient Its effect on coagulation should cease within a reasonable period of time following discontinuance of the medication or be rapidly reversed by the use of a suitable nontoxic antagonistic agent It should not produce cumulative or toxic side effects on repeated administration Adequate therapy with the agent should be economically reasonable and its therapeutic value must be clinically established

No single anticoagulant is available at the present time which fulfills all of the previously described ideal conditions The two types of drugs which are used as anticoagulants are represented by the rapidly acting, naturally occurring heparin

absorbed from the gastrointestinal tract following oral administration, they are produced synthetically and are reasonably economical even for long term medica tion A disadvantage of this group of agents is that, although in a single individual the response to a given dose is rather predictable, *there is considerable variation* between individuals in the response to a given standard dose In some patients routine dosage schedules tend to be cumulative, resulting in excessive therapeutic effect The effectiveness of the agents as anticoagulants must be determined by the prothrombin clotting time test, which requires adequate technical laboratory facilities *The therapeutic index of this group of agents is low* compared to that of heparin

Adequate anticoagulant therapy with the coumarin and indandione com pounds is present when the prothrombin level is 20 to 30 per cent of normal There is a tendency for patients to develop hematuria and to bleed *spontaneously from* mucous membranes if excessive hypoprothrombinemia is present Therefore all patients undergoing therapy with these drugs should have routine urinalyses for blood cells as well as adequate laboratory and medical supervision

The coumarin and indandione drugs produce their effect on the coagulation of blood by competing with vitamin K in the liver and thereby inhibiting the pro duction of prothrombin by the liver It has also been demonstrated that Dicumarol *inhibits the formation of convertin or proconvertin Usually the degree of hypo*-convertinemia parallels the hypoprothrombinemia These drugs are commonly

degree of effect of the test The Lee White hrombin has been ex cessively reduced by the drugs *The lack of effect of these agents on the Lee* White clotting time of blood led to some early skepticism of these drugs as in vivo anticoagulants Actually, the whole blood clotting time in patients who have been treated with the hypoprothrombin inducing drugs is prolonged if the test is conducted in siliconized glass tubes Under these conditions the whole blood clot ting time may be used as an index of therapeutic effect and has been advocated as an accurate test of the degree of anticoagulant activity

Dangers —The only toxicity which has been demonstrated as the result of ad ministration of the hypoprothrombin inducing drugs is that of excessive *lowering of the circulating prothrombin with resulting spontaneous* hemorrhage Five per cent of the patients who receive these anticoagulants develop hemorrhagic signs which are mild and readily controlled About 2 per cent of the patients develop severe hemorrhage which necessitates prompt attention The treatment of exces sive anticoagulant effect from these agents involves administration of fresh whole blood for replacement purposes *and the administration of* vitamin K_1 as the most effective antagonist to the action of the drugs *A rare* patient may not respond to vitamin K_1 but will respond to vitamin K_1 oxide Intravenous administration of vitamin K_1 produces its effect on the hypoprothrombinemia in approximately 6 hours The rapid recognition of impending excessive anticoagulant effect is therefore imperative *It is recommended that all ambulatory patients receiving* these drugs be instructed regarding the possibility of excessive drug effect

Lee White method Two types of dosage schedules are suggested Heparin may be administered intravenously in a dose of 50 mg every 4 hours or in a dose of 100 mg every 6 hours depending upon the results of a whole blood clotting time test performed at the bedside just prior to each additional dose If the clotting time is less than 2 times normal, the next dose is increased by one third to one half If the clotting time is more than 2½ times normal the next dose is reduced by one third to one half If the clotting time is between 2 and 2½ times normal the regular dose is repeated

UNTOWARD EFFECTS —It is interesting that temporary elevation of the clotting time to as much as 10 times the normal value will not result in spontaneous bleeding if the vasculature is grossly intact Prolonged heparinization for several days may lead to bleeding from mucous membranes In the presence of active bleeding heparin is contraindicated as it will intensify the bleeding All of the known pharmacologic effects of heparin can be specifically neutralized by administration of protamine sulfate toluidine blue or hexadimethrine bromide (Polybrene) These compounds react with the electronegative radicals of heparin thereby abolishing its effect Protamine sulfate is prone to produce severe hypotension and toluidine blue produces varying amounts of methemoglobinemia which may result in hypoxia Hexadimethrine bromide is the heparin antagonist of choice because it is notably free of toxic effects Hexadimethrine 1 to 2 mg as a solution of 1 mg per milliliter in isotonic saline when administered slowly intravenously will neutralize the effect of 1 mg (100 units) of heparin In excessive dosage hexadimethrine has been shown to produce an anticoagulant effect in animals It is indicated as a heparin antagonist when emergency surgery is necessary on heparinized patients It is commonly used following extracorporeal circulation in open heart surgery for heparin neutralization The effect of all heparin antagonists is determined by the Lee White clotting time test

Only about one fifth the injected dose of heparin is excreted in the urine therefore the presence of kidney disease does not contraindicate the temporary use of this drug No specific information is available concerning the prolonged use of heparin in the presence of kidney disease Liver disease unless accompanied by hypoprothrombinemia likewise does not contraindicate the use of this drug with adequate laboratory control

DEXTRAN —Several synthetic heparin like drugs have been developed in the laboratory Of these only dextran sulfate is currently in use Dextran sulfate is not currently available in the United States but has been used extensively in England where it was developed Its anticoagulant properties are identical with those of heparin Prolonged use of dextran sulfate may lead to the development of alopecia a side effect which has occurred with other synthetic heparin like anticoagulants and has precluded their use in this country

Coumarin and Coumarin like Drugs.—Following the discovery of Dicumarol seven additional compounds have become available which have a mechanism of action similar to that of Dicumarol All these compounds are of either the coumarin or the indandione type of structure They are all used for the same purposes and differ from each other mainly in their dose and onset and duration of action The advantages possessed by this group of agents are that they are readily

tinued when the prothrombin clotting time has been properly prolonged This type of combined therapy is recommended in all cases of pulmonary embolism because of the imminent danger of additional emboli and infarctions However, such combined therapy should be considered in all patients who have a previous history of repeated thromboembolic episodes and in whom the clinical findings indicate the presence of a major thrombus In the absence of active bleeding, there is no hazard in the use of initial heparin therapy in any patient who is waiting for the onset of drug action from the administration of a hypoprothrombin inducing agent Combined therapy gives the patient the advantage of immediate and prolonged anticoagulant effect with minimal discomfort and maximal economy

Regimen of Combined Treatment The following schedule is recommended for routine use of combined heparin and coumarin or indandione drug therapy

1 Heparin (50 to 75 mg every 4 hours) is given intravenously for the first ... hypoprothrombin induc... e an average ... d) to 2 to 2½ times normal
2 Th... the oral rou... of ... do...
3 The daily maintenance dose is then determined in the following manner D... to adminis... between... tered ... of the daily dose is recommended If the prothrombin time is less than 10 per cent of normal, the drug is omitted for that day The daily dose may be administered in divided doses and given with food if the patient develops gastrointestinal complaints following medication The general trend in the prothrombin level as determined day by day will usually enable the physician to predict the need for alteration of the dosage Hyporeactors as well as hyperreactors should always be anticipated in any group of patients
4 Only after a stable dosage requirement is established may the laboratory prothrombin determinations be performed at less than daily intervals Urinalysis for the presence of hematuria should also be done at regular intervals ... continued for a minimum ... s of the thromboembolic ep... d throm boembolism or with ... vascular insufficiency, it is desirable to continue anticoagulant therapy on a long term basis

RATIONAL BASIS FOR NEW ANTICOAGULANTS

The excellent cooperative types of clinical studies which have established the rational for the use of the anticoagulant drugs have also stimulated researchers to attempt development of better anticoagulants As far as the hypoprothrombinemic agents are concerned, this trend has resulted in a longer list of available drugs as each year goes by However, these new drugs are essentially of similar chemical

CONTRAINDICATIONS.—The presence of liver disease contraindicates the use of the drugs which produce hypoprothrombinemia. Aged and debilitated patients generally require a significantly lower dose than is required by average, well developed persons. The compounds are excreted both as such and in the form of unidentified breakdown products. Therefore the presence of markedly impaired kidney function contraindicates the use of the drugs. The availability of adequate reliable laboratory facilities is a necessity and in their absence the drugs should not be used. Surgery should not be performed on patients receiving these drugs until the prothrombin time has been restored to near normal by the use of vitamin K_1. Any pre existing defect in blood coagulability, such as disorders which manifest purpura, contraindicates the use of anticoagulant drugs. Evidence of the loss of vascular integrity in the gastrointestinal tract which may be the consequence of the presence of ulcerative lesions also contraindicates the use of these drugs.

HYPOPROTHROMBIN-INDUCING DRUGS.—The eight hypoprothrombin inducing drugs which are in common use are bishydroxycoumarin (Dicumarol), cyclocumarol (Cumopyran), ethyl biscoumacetate (Tromexan Ethyl Acetate), warfarin sodium (Coumadin Sodium Prothromadin) acenocoumarol (Sintrom), phenindione (phenylindandione, Danilone Hedulin Indon) diphenadione (Dipaxin), and anisindione (Miradon). All of these drugs are administered orally except warfarin sodium which may also be given intravenously. The onset of therapeutic action following a single dose varies with the particular drug used and may be from 12 to 36 hours minimum with warfarin sodium, ethyl biscoumacetate or phenindione, to 72 hours maximum with bishydroxycoumarin. The duration of action following discontinuance of the drugs also varies with the different drugs and may be from a minimum of one day with phenindione and ethyl biscoumacetate to 15 to 20 days with diphenadione and cyclocoumarol.

The Anticoagulant of Choice. Of the several hypoprothrombinemia-producing drugs which are available for clinical use the agent which most nearly approaches the requirements of the ideal anticoagulant is warfarin sodium. However, since it is one of the newer of the anticoagulants, it has not undergone the test of time or use in the hands of numerous investigators. A principal desirable feature of warfarin sodium is that with proper laboratory control a stable effect on prothrombin clotting time can be readily achieved. Clinical results to date indicate that there is minimum variation between patients in dose requirements. The incidence of hemorrhage resulting from excessive anticoagulant effect following the use of warfarin sodium is no greater than for the other drugs of this group. The onset of action is relatively rapid, being as short as 12 hours following intravenous administration, but at least 24 hours following oral medication. Heparin may be used in conjunction with warfarin sodium if immediate anticoagulant therapy is desired and may be discontinued after 3 or 4 doses. Vitamin K_1 readily elevates excessive hypoprothrombinemia induced by warfarin sodium to safe levels in 6 to 12 hours.

COMBINED HYPOPROTHROMBIN INDUCTION AND HEPARIN THERAPY. Adequate clinical anticoagulant therapy can be obtained with any one of the hypoprothrombinemic agents. When rapid initiation of anticoagulant action is necessary, heparin may be given along with the hypoprothrombin inducing agent and then discon-

is biologically standardized in hemophilic human beings A *hemophilic patient* who has lost an excessive amount of blood by hemorrhage must be administered whole blood so that the multiple complications of excessive blood loss are prevented In the absence of hemorrhage or hemorrhagic signs, the prolonged prophylactic use of the antihemophilic globulin is of a questionable purpose

Vitamin K Deficiency —A deficiency of vitamin K may result in hemorrhagic disease It may be due rarely to dietary insufficiency but more commonly to the failure of intestinal flora to synthesize the vitamin (during antibiotic therapy) In sprue and celiac disease absorption of the vitamin from the bowel is impaired and in biliary obstruction the lack of bile in the intestine results in failure of absorption even in the presence of adequate quantities of the vitamin Finally, the vitamin may fail to be utilized in the presence of severe liver disease or in anticoagulant therapy with the coumarin like agents The lack of vitamin K results in a hypoprothrombinemia and, also possibly a hypoconvertinemia which, if sufficiently severe, will result in spontaneous bleeding from mucous membranes

VITAMIN K —The two synthetic, water soluble vitamin K preparations which are available for clinical use are menadiol sodium diphosphate and menadione sodium bisulfite They may be administered intravenously every 6 hours in a dose of about 75 mg, and in the presence of adequate liver function elevation of the prothrombin clotting time to safe levels may be expected in 12 to 18 hours Vitamin K_1 as phytonadione is also available for clinical use It is synthesized and is identical with the naturally occurring vitamin It is not water soluble but is available as an emulsion for intramuscular or intravenous use The hypoprothrombinemias which are not due to the presence of severe liver damage will respond to vitamin K_1 usually within 6 hours following the intravenous dose of 50 to 100 mg

Vitamin K Preparation of Choice In the presence of impending or actual hemorrhage resulting from lack of vitamin K, the drug of choice is phytonadione because of its more rapid action However, in the presence of vitamin K deficiency states, the water soluble forms are completely adequate Since the liver is the site of synthesis of prothrombin and probably certain other factors involved in the clotting mechanism the administration of the vitamin in the presence of severe liver disease may not result in the restoration of the deficient prothrombin

No toxic effects have been described as a result of the properly controlled therapy with either vitamin K or vitamin K_1 Therapy with these agents should be instituted only in the presence of a prolonged prothrombin clotting time and should be evaluated by repeated prothrombin time determinations There is no rationale for administration of vitamin K in the presence of normal prothrombin values

CARBAZOCHROME (ADRENOSEM) —Following experimental evidence indicating that adrenochrome shortens the bleeding time in normal animals, the use of a soluble and stable adrenochrome derivative, *Adrenosem*, has been advocated for the treatment of conditions where oozing of blood from inaccessible vascular beds is present Animal experiments indicate that parenterally administered Adrenosem will protect certain vascular beds (the hamster cheek pouch) from hemorrhage produced by topically applied snake venom Such experiments indicate that Adrenosem increases capillary resistance to such vascular injury

Table 48 Suggested Dosage Schedule for Anticoagulant Drugs

[illegible]	[illegible]	[illegible]
Acenocoumarol	30 (1st day) 20 (2nd day)	2 8
Phenindione	200 300	50 100
Diphenadione	20 30	5 15
Anisindione	300 (1st day) 200 (2nd day) 100 (3rd day)	75 100

structure and biologic and toxicologic action Any further development of such drugs would be significant only if the possibility of hemorrhage from excessive dosage was considerably less than that of the existing members of this group of drugs Attempts to develop substitutes for heparin which possess heparin like activity have so far been discouraging, and so there is no list of such drugs However a heparin substitute provided it had no greater toxicity than that shown by heparin and particularly if it were orally effective would be a highly desirable therapeutic tool

The final answer as to whether the practicing physician should transfer from a drug with which he has had experience to one of the newer drugs rests on the appearance in the literature of well controlled, extensive clinical studies which conclusively demonstrate that the new drug possesses more of the attributes of the ideal anticoagulant"

COAGULATION-PROMOTING AGENTS

Certain hemorrhagic disorders have been shown to be the result of deficiency of one or more factors involved in the coagulation of blood, for which specific drug therapy other than whole blood transfusion, is available Among these diseases are the following true hemophilia, hyperheparinemia, hypoprothrombinemia resulting from liver damage or vitamin K deficiency Drug therapy of these disorders is not intended to produce active clotting in the vasculature but rather is intended to correct the deficiency and thereby restore the normal body defense against spontaneous hemorrhage

Hemophilia —Hemophilia is a sex linked hereditary disease characterized by a deficiency of circulating antihemophilic globulin Excessive hemorrhage may result from only minor lacerations of the vascular bed and generally requires whole blood transfusion to replace the loss of blood It is interesting that small amounts of whole blood will partially restore the clotting power of hemophilic blood, but even multiple transfusions do not completely restore the clotting power to normal The antihemophilic globulin is available as the globulin fraction obtained from pooled human plasma by the low salt, alcohol fractionation method of Cohn It

clot promoting agent may be washed away before it can produce its effect When thrombin is applied topically to denuded areas in the presence of blood, it is inactivated by antithrombin in the blood and adsorbed to the fibrin so there is little danger of systemic absorption resulting in intravascular thrombosis Thrombin should never be injected intravenously as it will lead to widespread intravascular thrombosis and death within a few minutes

Russell Viper Venom and Trypsin—Many proteolytic enzymes have multiple effects on blood coagulation and resolution of clots Certain of these enzymes particularly that of the Russell viper venom (Stypven) and the enzyme trypsin are available for clinical use Minute quantities of these enzymes when added to blood *in vitro* are capable of substituting for thromboplastin and thereby promote the conversion of prothrombin to thrombin with the subsequent formation of a clot In contrast to this high concentrations of the enzymes have the reverse effect of inhibiting clot formation and also degrade fibrinogen The clinical value of these agents in hemorrhagic disease is not as yet established Clinically it appears that the topical use of the enzyme from the Russell viper venom offers no clot promoting benefits that could not be achieved more rationally by the use of topical thrombin

Sclerosing Agents—The vascular sclerosing agents act indirectly as clot producing agents The treatment of varicosities involves the use of the sclerosing agents These agents are strong irritants to the intimal lining of the blood vessel They produce sufficient irritation and breakdown of the intimal surface at the site of their injection so that clot formation is initiated These agents are most effective in the treatment of small varicosities remaining after surgery involving vein stripping or ligation

Two types of sclerosing agents are in common use The first and most widely used preparation is sodium morrhuate It is prepared from fish liver oils A rare patient will show a minor skin hypersensitivity to the preparation It is injected as a 10 per cent solution and the dose will vary from 0 1 ml for a small varicosity to 1 ml for a large varicosity Application of a pressure bandage immediately following the injection will facilitate adherence of the walls of the collapsed vein by the fibrin of the intravascular clot and thus ensure permanent obliteration of the vessel The second preparation is sodium psylliate, which is prepared from the oil of psyllium seed The preparation is used in the same manner as that described for sodium morrhuate It should be used in all patients who show sensitivity to sodium morrhuate

FIBRINOLYTIC AGENTS

A blood clot which has been formed in the vascular bed may undergo either resolution with no subsequent sequelae or organization with the subsequent formation of fibrous tissue When resolution occurs spontaneously, it is believed to be the result of the action of the lytic enzyme (fibrinolysin) This enzyme exists in inactive form as profibrinolysin in blood It is slowly activated by cell fragments

[illegible] nase

is an enzyme which is produced and secreted

tain strains of beta hemolytic streptococci The

OTHERS —Certain agents influence the normal ability of the capillaries to prevent the passive transfer of red blood cells through their walls Thus increased capillary permeability to red cells may result from vitamin C deficiency The use of ascorbic acid as a specific therapeutic agent in this disorder is classical However, certain cases of increased capillary permeability to red cells may not be controlled by the administration of vitamin C alone The flavone glycosides are known to influence favorably certain cases of increased capillary permeability The preparation in use is rutin It is usually administered orally in conjunction with ascorbic acid The exact mechanism of action of rutin on the capillary wall is not understood Several naturally occurring bioflavinoids are currently under clinical investigation as anti inflammatory and antihemorrhagic agents and show promise of a higher order of activity than that produced by rutin

The use of estrogenic substances in the management of uterine bleeding has been popular for many years Recent investigations have led to the use of these compounds in the management of epistaxis postoperative hemorrhage, and in urinary tract and gastrointestinal bleeding Although well controlled clinical studies are not available evidence obtained on dogs has established that intravenous estrogen produces a prompt (within 1 hour) increase in circulating prothrombin and accelerator globulin and a decrease in antithrombin activities of the blood Theoretically these changes tend to enhance coagulability of the blood thereby providing a rationale for the current, popular, short term use of estrogens in spontaneous hemorrhage Epistaxis or hemorrhage following adenoidectomy may be treated with a single dose of intravenous conjugated estrogens (20 mg)

COAGULATION PROMOTING AGENTS WHICH RESULT IN CLOT FORMATION

There is no substitute for the pressure of the surgeon s gloved finger and the hemostat for the prevention of gross bleeding from an exposed severed blood vessel However certain drugs are of great value to allay the continuous oozing of blood from denuded areas that become so troublesome to the physician and terrifying to the patient The agents to be described here are generally indicated only in those situations where mechanical hemostasis has not been or cannot be achieved either because of lack of accessibility or extensiveness of the bleeding area The combined use of pressure and an agent to promote clot formation is frequently advantageous

Thrombin —Bovine thrombin is available in lyophilized form for topical use to initiate clot formation In the presence of blood as a source of fibrinogen, the application of thrombin will result in the almost immediate formation of a clot When a pad of fibrin (fibrin foam) or an absorbable gelatin sponge (Gelfoam) or oxidized cellulose (Oxycel) is saturated with a solution of thrombin and the pad is placed over a denuded area which is oozing blood the pad acts as a preformed network to trap the blood The presence of thrombin immediately forms a clot which effectively seals off the bleeding area with a coating of normal blood clot Thrombin may also be instilled as a solution into the stomach to hasten the formation of a firm clot over a peptic ulcer which is oozing blood However, in the presence of an active flow of blood, this procedure may fail to be effective since the

clot promoting agent may be washed away before it can produce its effect When thrombin is applied topically to denuded areas in the presence of blood, it is inactivated by antithrombin in the blood and adsorbed to the fibrin, so there is little danger of systemic absorption resulting in intravascular thrombosis Thrombin should never be injected intravenously as it will lead to widespread intravascular thrombosis and death within a few minutes

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Streptokinase —Streptokinase is an enzyme which is produced and secreted into the nutrient medium by certain strains of beta hemolytic streptococci The

commercial preparation of streptokinase is extracted from such nutrient media along with an additional mixture of enzymes which are collectively called streptodornase These enzymes are capable of degrading many complex proteins into nucleotides and smaller protein fragments Streptodornase is of value clinically since it will depolymerize desoxyribonucleoprotein which is the principal component of thick purulent exudates Both streptokinase and streptodornase are standardized on the basis of units of activity Freshly prepared solutions of the lyophilized enzymes are effective in promoting the liquefaction of fibrin and exudates They are therefore used as a means of enzymatically debriding surface wounds Streptokinase has also been used to promote lysis of fibrin in the pleural space

The combination of streptokinase and streptodornase is used topically as a freshly prepared solution in phosphate buffer of pH 7 5 Depending on the amount of coagulum present a solution containing from 1 000 to 200 000 units of streptokinase with 250 to 50 000 units of streptodornase is applied once daily as a wet soak for a 4 to 6 hour period The preparation may be used in conjunction with antibiotic agents This preparation has recently been recommended for systemic intramuscular use to stimulate dissolution of fibrin and promote penetration of concomitantly administered antibiotics

Parenteral use of these enzymes leads to the development of antienzymes a rare allergic reaction of pyrogenic nature and mild tenderness at the injected site when administered intramuscularly Streptokinase should not be given to patients known to have blood clotting defects

Trypsin —Trypsin readily liquefies fibrin and will degrade hemoglobin Well formed fibrous tissue is not influenced by the enzyme Because of the fibrinolytic action of trypsin it is used as a means of enzymatic debridement of surface wounds For maximum activity it must be used in a buffer medium having a pH of 7 This is obtained by dissolving the pure crystalline trypsin (200 to 500 mg) in a phosphate buffer The solution is topically applied as a wet soak and is changed every 2 to 3 hours until satisfactory debridement is achieved Fresh blood contains a trypsin inhibitor (antiprotease) which effectively limits the activity of the enzyme

SELECTED REFERENCES

Alexander B Coagulation Hemorrhage, and Thrombosis New England J Med 252 43? 484 5?6, 1955

Barrone A M Varicose Veins and Venn [illegible] 1948 [illegible]

Intern [illegible]

Marple [illegible]

Nichol [illegible]

Owren [illegible]

Tocant [illegible] Methods of Study New York 1955 Grune & [illegible]

Wenthert, A., and Nilsson I M Thromboplastin and Russell Viper Venom, Scandinav J Clin & Lab. Invest. 7: Supp 15 6, 1955

Wright I S Pathogenesis and Treatment of Thrombosis, New York, 195?, Grune & Stratton, Inc.

THE CHOICE OF DRUGS IN OBSTETRICS AND GYNECOLOGY

M Edward Davis, M D, and
Nicholas W Fugo, Ph D, M D

INTRODUCTION

The practice of obstetrics and gynecology employs the same therapeutic armamentarium utilized in the other recognized specialties of the medical arts

Obstetrics —In obstetrics, however, a unique situation exists, for in the administration of a drug one must consider not only its effect on the mother but also its possible reaction on the developing conceptus This is important for several reasons Although all therapeutic agents are not capable of transmission across the placental membranes, the vast majority of drugs do affect the fetus in one way or another

The inability of a drug to pass into the fetal circulation is desirable so that effective and therapeutic levels may be attained in the maternal organism without the danger of toxic levels in the fetus This may be true of such agents as the barbiturates which normally are detoxified by the liver However, the inability of a drug to be transported across the placental barrier does not assure complete protection to the unborn child Drugs which induce uterine contractility may alter the uterine blood supply and interfere with placental circulation to such an extent as to produce anoxia in the fetus with serious damage or even fetal death This is true of such drugs as pituitary extracts or ergot derivatives

Furthermore, the physiologic changes of pregnancy may induce an altered response to some therapeutic agents An example of this phenomenon is the greatly increased tolerance of the pregnant female to the oral administration of large doses of the synthetic estrogen, diethylstilbestrol Care must also be taken in prescribing drugs to lactating mothers since some agents are secreted in the milk and may cause toxic effects in the newborn infant

The recent advances in the medical sciences have made it possible for many women with chronic diseases to reach the reproductive age and to bear children This is especially true of females who develop diabetes mellitus in childhood and in women with Addison s disease These advances have altered our concepts of the reproductive process and have added new problems in the care of these chronically ill patients and their offspring

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SELECTED REFERENCES

Alexander, B Coagulation Hemorrhage, and Thrombosis, New England J Med 252 432, 484 526, 1955

Barrone, A M Varicose Veins and Venous Thrombosis of the Lower Extremity, Chicago, [illegible]

[illegible] 201, 1955

Tocantins, L M The Coagulation of Blood, Methods of Study, New York, 1955, Grune & Stratton, Inc

Wenckert, A , and Nilsson, I M Thromboplastin and Russell Viper Venom, Scandinav J Clin & Lab Invest 7 Supp 15, 6, 1955

Wright, I S Pathogenesis and Treatment of Thrombosis, New York, 1952, Grune & Stratton, Inc

necessary to prescribe calcium and phosphorus if the patient consumes sufficient milk and milk products In the event that these foods cannot be tolerated, it is necessary to supplement diet with these minerals It is customary to provide additional amounts of vitamins A and D throughout pregnancy even when the dietary intake is otherwise considered adequate

Specific Difficulties —

MORNING SICKNESS —In about half of all pregnant women the early weeks of the pregnancy are associated with 'morning sickness,' nausea with or without vomiting or a distaste for many foods This disorder is probably the result of the altered metabolic processes of gestation If it is neglected, this complication may result in serious electrolyte and fluid imbalances which will necessitate hospitalization Morning sickness usually disappears by the end of the first trimester, and if properly treated it will remain a minor discomfort

The management consists of reassurance, fresh air and moderate exercise, and dietary regulation The patient is advised to eat small amounts of dry food at frequent intervals, to avoid greasy foodstuffs, and to alternate dry feedings and liquids The odors of cooking should be eliminated, and the desire for unusual foods may be encouraged Emotional factors do play an important role in morning sickness

Drugs are of some benefit if used judiciously There are a number of antiemetic agents available today which are effective in many cases These are discussed in Chapter 20

One of the most practical agents from the viewpoint of simplicity and cost is a mixture of phenobarbital either in 15 or 30 mg doses, with 7 5 mg of belladonna This mixture when administered 2 or 3 times a day is a satisfactory adjunct to wet and dry feedings

If these simple measures are inadequate and the patient is unable to tolerate any food if she becomes dehydrated and exhibits symptoms of electrolyte imbalance she should be hospitalized immediately and parenteral solutions administered Blood electrolyte levels should be determined and deficiencies corrected The patient should be heavily sedated with Amytal Sodium 0 2 Gm intramuscularly at 3 or 4 hour intervals In most cases this therapeutic regimen is sufficient to correct the disorder The patient should not be allowed visitors or phone calls The room should be kept darkened and all outside stimuli should be avoided It may be necessary to institute tube feeding in severe cases Rarely is it necessary to interrupt the pregnancy to cure the patient

CYSTITIS AND PYELITIS —Cystitis occurs predominantly in the puerperium rather than in the antenatal period If it occurs before delivery it often consists of mild irritation of the trigone On the other hand, when it occurs post partum, due to the trauma of delivery, it is a much more serious complication Not only is there edema but in some cases extravasations of blood This may be sufficient to cause obstruction of the urethra and acute retention These conditions frequently lead to a true cystitis If the bladder has become overdistended and the patient does not void spontaneously, after a maximum of 3 catheterizations at intervals of 6 to 8 hours, it is wise to insert an indwelling catheter for a period of approximately 72 hours to ensure rest to the bladder and its complete emptying

Even the lifesaving procedure of blood transfusion to a young girl may in later life be hazardous to her reproductive performance The administration of unsuitable blood may induce Rh antibodies in a young woman who marries an Rh positive husband She may deliver erythroblastotic infants, some of whom may be stillborn or fail to survive in spite of modern therapy in the form of exchange transfusions

Other physiologic changes in the pregnant woman must be considered when using drug therapy The emptying time of the stomach is increased, allowing administered drugs to remain in the stomach for a longer time This slows the development of the action of orally administered drugs Weight gain, water retention, the elevation of the basal metabolic rate, altered kidney function the retention of nitrogen, as well as other alterations in metabolic patterns in pregnancy, influence the selection and utilization of therapeutic agents

Gynecology —The problems in gynecology, on the other hand, are essentially the same as those encountered in the fields of surgery Pre and postoperative care present no problems unique to gynecology Most therapeutic agents utilized are in the nature of anesthetics, sedatives, replacement fluids, and hormones The proximity of the ureters, bladder, and rectum to the pelvic organs concerns the skills rather than special therapeutic agents

NORMAL PREGNANCY

Principles —In no specialty of medicine is the concept of preventive medicine more important than in the care of the pregnant woman Prenatal care has a dual role of assisting the patient to meet the demands of pregnancy and of anticipating and preventing possible complications The first visit to the physician should include a careful history of previous gestations and systemic diseases as well as a complete physical examination The physical evaluation should include blood and urine examinations and routine chest x-ray Inoculation against poliomyelitis is recommended for the incidence of this infection is higher in pregnant women than in the general population A history of rheumatic or congenital heart disease should be carefully evaluated, since heart disease is becoming one of the important causes of maternal death The patient is usually advised to return at 3-week intervals during the first 7 months of gestation, at 2 week intervals during the eighth month, and weekly during the last month of pregnancy

The present philosophy of maternity care is that it is a physiologic process and that it need not be enmeshed in obsolete taboos, fears, and fancies To this end the education of mothers and fathers concerning the reproductive process is of paramount importance An intelligent discussion with a patient concerning some new complaint may be more rewarding than the administration of the latest tranquilizer Too often in the care of pregnant women, drugs take the place of intelligent medical guidance

Nutrition is of the utmost importance in pregnancy An adequate diet to meet the physiologic demands of the mother and the growth needs of the baby will decrease the likelihood of maternal complications and increase the chance of a healthy baby Diet instruction is an essential part of prenatal care It is rarely

CONSTIPATION One of the most common complaints of pregnant women is constipation This is not serious, but it is troublesome and should be corrected Furthermore it tends to increase the incidence of hemorrhoids Cathartics should be avoided during pregnancy although in the past the hazards of mild purgatives to the pregnancy have probably been overemphasized

Frequently, small doses of mineral oil or preparations containing agar and oil will promote ease in evacuation, with little or no harm There is a theoretic objection to their use in that some fat soluble vitamins are taken up by these compounds More recently surface active (wetting) agents which soften the stool for easy passage have been developed These work well in the ambulatory patient Dioctyl sodium sulfosuccinate in doses of 100 mg once or twice daily with an adequate intake of water will alleviate most cases of constipation encountered in pregnancy provided there is no organic disease The use of a glycerin suppository on awakening in the morning may prevent excessive straining

Bisacodyl Recently there has appeared a promising new synthetic compound Bisacodyl which is colorless tasteless and practically insoluble in water and alkaline solutions Its action is dependent on contact with the colonic mucosa It can be administered orally or by rectal suppository Its action is to induce normal peristalsis throughout the colon and it has little or no effect on the small intestine It is an effective laxative in all types of constipation It may be used in preparation for operations or post partum The suppositories may be used to replace enemas It is available *in two forms* (1) enteric coated tablets swallowed whole in dosage of one to two 5 mg tablets or (2) 10 mg suppositories The suppositories are effective in 15 to 60 minutes The compound apparently has little or no toxicity for it is not absorbed

HEMORRHOIDS —In the later months of pregnancy hemorrhoids are frequently a disturbing complication These are best treated by bed rest and various types of rectal suppositories of which there are many on the market In recommending suppositories for this condition it is wise to avoid those containing local and topical anesthetics usually but not always easily identified by the caine' suffix in their names *Many of these are sensitizing* agents and always present the danger of allergic reactions We have had satisfactory results with suppositories containing a mixture of opium and belladonna If the hemorrhoid has been recently thrombosed great relief can be provided by the evacuation of the clot The pain of hemorrhoids associated with edema can be relieved by ice packs to the rectum

LEG CRAMPS —In recent years much has been written regarding the therapy of leg cramps commonly encountered in the last trimester of pregnancy It is thought by some that this symptom develops as the result of an imbalance of the calcium and phosphate ions This condition is extremely painful and difficult to avoid The elimination of foods high in phosphate content may be of some value Gen eral measures such as the avoidance of chilling and the application of heat are helpful in some cases

HEARTBURN —The delay in the emptying time of the stomach in the latter months of pregnancy may cause *heartburn in* ients This co be treated by the use of aluminum hydroxi Sodium b

This also prevents overdistention and residual urine in the bladder The patient should take large amounts of fluids and it is wise to use sulfisoxazole in 0 5 Gm doses 4 times a day prophylactically

PYELOURETERITIS —There is about a 2 per cent incidence of pyeloureteritis during pregnancy The process usually is bilateral but when unilateral it is more often right sided. It is usually acute The patient complains of costovertebral angle tenderness burning on urination, frequency and not infrequently she develops a rise in temperature Diagnosis is easily and quickly made by a microscopic examination of a catheterized urine specimen This will contain clumps of red and white cells and frequently bacteria Once the diagnosis is established it is wise to culture the urine and to determine antibiotic sensitivity

Most urinary tract infections will respond to sulfisoxazole in dosage of 1 Gm 4 times a day If the patient cannot tolerate the oral administration the drug may be given intravenously diluted 2 Gm to 1 000 ml of 5 per cent dextrose in water While this drug is of low toxicity the usual precautions should be observed as with other sulfonamides The patient should be given large amounts of fluids Persistence or recurrence of symptoms and the presence of bacteria in the urinary cultures demonstrate resistance to this therapeutic agent Oxytetracycline is a valuable agent in such cases because of its truly broad spectrum of activity The usual dosage is 250 mg 4 times a day

ANEMIA OF PREGNANCY —The determination of hematocrit and hemoglobin values during pregnancy is an important part of prenatal care It should be repeated at 3 month intervals and it is desirable that the last determination be made within 4 weeks of the expected date of confinement The physiologic anemia which normally develops about the end of the second trimester of pregnancy as a result of blood dilution may be sufficiently marked to warrant therapy The normal hematocrit range for pregnant women is between 35 and 45 per cent The lowest value will be obtained at approximately 30 to 32 weeks gestation If the hematocrit value drops below 32 per cent therapy is indicated Most anemias of pregnancy are due to iron deficiency which is easily remedied by the oral administration of iron One of the most satisfactory preparations for this purpose contains ferrous sulfate with molybdenum oxide The usual dose is 1 to 2 tablets 3 times daily

There are occasional patients who do not do well on oral iron therapy This may be due to gastrointestinal upsets or the patient may be lax in taking the medication, or circumstances may require more rapid accumulation of iron stores than is possible by the oral route Under these conditions intramuscular administration of iron may have excellent results The compound of choice is a solution of iron dextran complex which provides 50 mg of ferrous iron per milliliter of solution The response obtained is reported as equal to intravenous injections The average dose is 500 mg of elemental iron per week If the anemia is not markedly improved in a reasonable period of time a complete blood study is indicated to determine the nature of the anemia If the patient has difficulty with ferrous sulfate frequently preparations of ferrous gluconate or ferrous glycinate can be better tolerated Rarely is it necessary to treat iron deficiency anemia with blood transfusion

Many physicians prefer the local infiltration of the perineum with anesthetic agents or pudendal block because of the simplicity and safety of these procedure However these methods do not provide adequate pain relief for many patients

In our clin c the anesthetic of choice is saddle block The agent employed is hyperbaric Nupercaine solution in 2 5 mg dosage The anesthetic is not administered until the patient is in the second stage of labor and can be delivered immediately if necessary The subject is placed in the sitting position with the back arched outward and head down A 22 gauge spinal needle is introduced at the level of L 3 or 4 The Nupercaine is injected over a 3 second interval only durin a period free of uterine contractions The needle is left in place for exactly 10 seconds after the initiation of the injection The needle is withdrawn and the patient is told to straighten her back The subject remains in the sitting position for exactly 20 seconds longer she is then placed flat with the head elevated by means of a pillow A period of 5 to 10 minutes is allowed to elapse to stabilize the anesthetic level The fetal heart tones and blood pressure are checked at frequent intervals Rarely hypotension occurs and this is easily corrected by placing the patient in the lithotomy position If this rigid routine is followed the he ght of the level of anesthesia is limited to the level of the umbilicus The perineum is well anesthetized to permit major operative procedures Exploration of the birth canal and uterus can be performed with little or no discomfort to the patient

In our experience with normal cephalic deliveries this is the anesthetic of choice We have successfully performed over 22 000 saddle block anesthetics with no known sequelae of a serious nature An occasional patient complains of post anesthetic headache which may last two or three days These are best treated by having the patient lie flat in bed

Saddle block anesthesia is not recommended for deliveries where marked uterine relaxation is necessary for the successful delivery of breech multiple pregnancy or abnormal presentations These procedures usually necessitate inhalation anesthetics and deep surgical relaxation The safest agent under these conditions is open drop ether When this anesthetic agent is used premedication is necessary If the patient has taken food in the period immediately prior to the delivery it may be wise to empty the stomach by gavage or induced vomiting since nausea is a common concomitant and aspiration an important hazard Furthermore the peril of postpartum hemorrhage from an atonic uterus must be considered Fetal anoxia can also occur and must be dealt with by means of tracheal catheterizat on and oxygen administration

Oxytocic Drugs —

General Considerations —The human uterus is capable of responding to many stimuli Nervous chemical and even mechanical agents can produce marked reactions many of which are poorly understood physiologically While the myometrium is richly supplied with autonomic nerves the response of the uterus is apparently dependent on the titer of estrogens and progesterone

Normal uterine motility is dependent upon the presence of calcium and estrogens The addition of stimulating drugs may alter these patterns or produce marked contraction of the entire organ Under normal conditions in the presence

compounds should be avoided since these are absorbed and if retained favor the development of edema

PTYALISM —Rarely is a pregnant patient bothered by excessive ptyalism This condition is not serious but it is uncomfortable, these patients may be seen walking around holding a receptacle into which to expectorate Many remedies have been suggested, none of which correct the condition The simplest and probably most effective is tincture of belladonna Dosage can start with 1 or 2 drops in a half glass of water 2 or 3 times per day This amount can be increased, but it should not exceed 10 drops per dose Frequently the side effects of the belladonna are more disturbing than the ptyalism so that the patient stops the medication of her own accord and says no more about her troubles

Analgesia During Labor —Drugs for the relief of the discomfort of labor are legion Hardly a month goes by without claims for an ideal substance which will convert labor into a pleasant experience without hazard to mother or baby The large number of amnesic analgesic and anesthetic drugs available to the practitioner bears mute but substantial evidence that the answer to our age old problem is not to be found in drugs alone

GENERAL CONSIDERATIONS —The present pattern of maternity care is designed to remove all fears concerning this fundamental physiologic function to prepare the individual by lectures, discussions and exercises to look forward to the most important episode in her life and to allow her to participate in this wonderful emotional experience to the limit of her capabilities Obviously such an enlightened approach toward labor places little stress on pain relief and great emphasis on education It is hoped that the old goal of removing every vestige of discomfort and blotting out all memory of life s greatest experience has passed

Patients should be told that labor contractions will become uncomfortable as active labor progresses, that we have a number of drugs available which will relieve such discomfort and that they can be administered with safety to mother and baby This will decrease the need for sedative and pain relieving drugs early in the course of the labor, which occasionally may interfere with its normal progress Furthermore, it will prevent apprehension on the part of the patient that she may not be given pain relief

Dangers All pain relieving drugs in labor exercise a double threat, to the mother and to her baby They may interfere with uterine activity, prolonging labor and thus occasionally predisposing to difficult operative procedures They interfere with the establishment of normal respiration by the newborn at birth, necessitating measures for resuscitation and for combating anoxia The choice of the drug, the amount administered and the period in labor when it is given, all influence its undesirable sequelae General anesthetic agents likewise tend to increase the incidence of respiratory difficulties in the newborn

OPIUM DERIVATIVES AND SYNTHETIC SUBSTITUTES —The opium derivatives such as morphine and codeine and their synthetic substitutes, methadone and meperidine, are widely used in obstetrics The main function of these drugs is the alleviation of pain associated with uterine contractions of labor In using a drug for this purpose the ideal agent would be one that would have marked analgesic activity with little or no depressant action on fetal respiration or inhibiting action

At times, because of the injudicious or untimely administration of the dr in a uterus overdistended because of twins or polyhydramnios, or deep surgical an thesia, the myometrium will fail to respond to the oxytocic drug If the uteru found to be flaccid, a second dose of ergonovine may be administered intravenou *It is our practice to repeat the oxytocic drug only once* When the bleeding p sists, it is essential that other factors responsible for postpartum hemorrhage determined The uterus and birth canal must be carefully explored Retain placental fragments must be removed There must be no trauma to the uterus cervix The birth canal must be free of lacerations *If, after all these possibilities* eliminated hemorrhage still persists, a uterine pack may be inserted If the patie bleeds through the pack hysterectomy should be performed Fortunately this an extremely rare complication, but one should always be aware of the possibili

It is mandatory in the care of pregnancy and labor complications associat with excessive bleeding to start an intravenous drip of saline or 5 per cent dextro solution and to use blood in ample amounts when necessary These should alwa be available

Pituitary Materials —Extracts of the posterior lobe of the pituitary ha three types of activity vasopressor, antidiuretic, and oxytocic There are on two principles, however, one of which, in the human, exerts oxytocic as well as vas pressor and antidiuretic actions and the other of which is entirely oxytocic Bot are inactive orally and must be given parenterally

The response of the human myometrium to posterior pituitary extracts is ex tremely variable, depending on many factors, hormonal titers for example I general, large doses may produce uterine tetany which may last for as long as 1 minutes, *followed by gradually increasing clonic contractions, while smaller dose* produce only clonic contractions

Posterior Pituitary Extract The major use of posterior pituitary extracts i obstetrics is in the prevention of postabortal or postpartum uterine atony It i more effective in postabortal states than is ergonovine but less effective than th *latter drug post partum It can be given subcutaneously or intramuscularly* quit safely in doses up to 10 units It must be used in much smaller doses, however when given intravenously If given without due respect for its unpredictability o action, this procedure is fraught with danger, it may produce uterine rupture or fetal death due to anoxia

Pitocin Pituitary induction of labor should never be attempted without com petent personnel in constant attendance The preferred method is the dilution of 10 units of Pitocin in 1,000 ml of 5 per cent dextrose in water It should be given intravenously extremely slowly because of its greater safety and controlla bility It should always be started in extremely small doses and increased cau tiously

Pitocin drips should never be used during labor if there is any evidence of fetal distress Care should be taken that no cephalopelvic disproportion or ab normal presentation exists *Because of the danger of* uterine rupture, labor must never be induced with Pitocin if the patient has had cesarean section in a previous pregnancy Because of increased scar tissue in the uterus it is also contraindicated in patients of high parity (5 or more) or in those over 35 years of age *If the pa*

of estrogens the uterus has normal rhythmic contractions which are initiated in the fundus in the region of the fallopian tubes and course down the corpus toward the cervix. The normal progress of labor depends on the rhythmicity of the uterine contractions as well as their increasing frequency, duration, and intensity. It is believed that normal uterine motility and progress in labor are influenced by the metabolism of the steroid hormones which control the reproductive function. There is evidence that the responsiveness of the uterus can be greatly enhanced by the administration of ionized calcium salts.

The oxytocic drugs are those that promote uterine contractions. They are most often used in the management of the placental stage of labor and in the postpartum period. These drugs are derivatives of ergot, posterior pituitary extracts, or synthetic preparations. In recent years the posterior pituitary extracts have gained renewed popularity for the induction of labor. The dangers of their use will be discussed later.

ERGOT ALKALOIDS.—Ergot is a fungus (*Claviceps purpurea*) which grows on rye and certain other grains. Ergot contains a great number of pharmacologically active substances. The ergot alkaloids occur in pairs which are optical isomers, the levo forms are active, having oxytocic properties while the dextro forms are inactive. The most active of these is ergonovine, a derivative of lysergic acid.

Ergonovine. Ergonovine is the hydroxyisopropylamide of lysergic acid. The maleate, the only salt that is water soluble, is used. In therapeutic doses (0.2 to 0.4 mg.) it induces tonic uterine contractions on which are superimposed clonic contractions. These are the result of direct muscle stimulation. Side effects are rare after therapeutic doses. Elevation of blood pressure may be encountered rarely and is more likely if spinal anesthesia is used. Vasoconstriction, sufficient to cause gangrene, may occur, but ergonovine is much less toxic in this regard than the other ergot alkaloids, and for all practical purposes there is no danger of gangrene when the drug is used as an oxytocic.

In our institution ergonovine maleate is used routinely in the management of the third stage of labor. Immediately after the anterior shoulder of the infant is delivered under the symphysis, 1 ml. of solution containing 0.2 mg. of the drug is injected intravenously. Approximately 30 seconds is allowed to elapse, after which the delivery is completed slowly and deliberately. In many cases the remainder of the infant will be delivered by the contraction of the uterus induced by the ergonovine. The completion of the birth of the infant is followed by the expulsion of the placenta by Crede's maneuver with a minimal amount of blood loss in most instances. Infrequently, and especially if the delivery of the infant is rapid, the placenta may be trapped in the lowermost portion of the corpus and lower segment. If this occurs, it is a simple maneuver to slip the hand into the cervix like a shoehorn and, with moderate traction on the cord, ease the completely separated placenta out of the birth canal.

On rare occasions, the placenta fails to separate completely spontaneously. If uterine bleeding occurs under these circumstances we do not hesitate to invade the uterus, removing the adherent placenta manually with sterile precautions. In most cases complete removal of the placenta will allow the uterus to contract and terminate the bleeding.

Epinephrine.—It has been suggested that epinephrine is an effective ag for the relaxation of contraction rings during labor, but clinical experience d not bear this out There is also the danger that when this drug is given by intr muscular injection in doses adequate to relieve contraction rings or tetany a pr longed period of uterine atony with hemorrhage may follow

In clinical practice, when local anesthesia is employed epinephrine is fr quently added to the anesthetic agent for purposes of prolonging its effect the concentration of epinephrine is 1 200 000, and 50 ml of the anesthetic is a ministered the patient receives a dose of 0 25 mg of epinephrine In many ca this is sufficient to interfere with the mechanism of labor and may cause prolong tion of the second stage and possibly uterine atony and hemorrhage

Norepinephrine.—Norepinephrine has become popular for the support blood pressure due to surgical or anesthetic shock This substance, unlike ep nephrine induces an increase in uterine contractility and in this event it is poss ble that the increased uterine contractions, in the presence of depressed bloo pressures will further embarrass the fetus With this possibility in mind norep nephrine if used at all should be used with great caution in the gravid woman

Relaxin.—In recent years relaxin (Releasin) the water soluble ovarian extra first described by Hisaw as the hormone responsible for the relaxation of pub ligaments in the pocket gopher and guinea pig has been further purified and its u in women during pregnancy has been advocated

The claims made for this substance are rather broad It is stated that relax can halt premature labor and facilitate it at term when labor is prolonged or diffi cult because of cervical dystocia There have appeared innumerable reports on th subject In our hands and in personal communication with Caldeyro-Barcia th substance is without therapeutic effect in altering the course of labor Only tim and much carefully conducted clinical research can determine the value of thi agent

TOXEMIAS OF PREGNANCY

The toxemias of pregnancy are still major complications of human reproduc tion and are responsible for considerable maternal and perinatal mortality Th hazards to mother and baby have been reduced appreciably in recent years largely as a result of the prevention of the convulsive stage eclampsia by intelligent pre natal care and improvement in obstetric practice The cause of pre eclampsia i unknown and thus there are no specific therapeutic agents for its prevention or cure

Toxemias of pregnancy are classified into two groups Pre eclampsia and eclampsia have their origin in pregnancy and are true pregnancy toxemias Hy pertensive renal disease exists prior to the onset of pregnancy and is aggravated by the metabolic alterations of gestation The incidence of toxemia is 6 or 7 per cent distributed equally between the two groups

Pre eclampsia and Eclampsia.—Pre eclampsia and eclampsia are complications of the last 16 weeks of pregnancy They occur most commonly in the young primigravida although they may complicate any gestation and at any age Al though the etiology is definitely unknown present thinking suggests that they may

tient has an extremely irritable uterus or is already in labor Pitocin induction must be used with great caution if at all

Pitocin induction is not likely to be successful unless the state of the cervix is favorable for the onset of labor A favorable or ripe cervix is soft the cervical canal is completely effaced and its thickness is no more than 1 cm These conditions apply to primiparas and multiparas except that cervical dilation of at least 2 cm should be present in the multipara before induction is attempted Effacement of the cervix is not a prerequisite in the multipara as in the primigravida Rupture of the membranes will increase the chances of success with Pitocin drip However the rupture of the membranes should not be attempted in the presence of an unfavorable cervix unless abdominal delivery is contemplated within 24 hours In many instances unsuccessful Pitocin inductions will be followed by evidence of fetal distress This may be indicated at the time of delivery by meconium stained amniotic fluid

Synthetic Oxytocic Drugs The cost and the unpredictable supply from Spain and Russia of ergot as a source for ergonovine have spurred organic chemists to study the ergot alkaloids with the hope of developing synthetic preparations In recent years the elucidation of the chemical structure of lysergic acid has led to intensive investigation of methods for synthesizing this basic unit of the ergot alkaloids

One of the new oxytocic drugs is methylergonovine tartrate a partially synthesized derivative of lysergic acid which is closely related to ergonovine and is quite similar to it in its action Clinical observations have indicated that the intensity and duration of its oxytocic activity are similar to those of ergonovine Its action and uses also closely approximate those of ergonovine its therapeutic use and dosage are the same

Largely through the work of du Vigneud and his associates it was possible to isolate pure oxytocin from the posterior pituitary gland and to determine its precise structure Synthesis followed rapidly on the heels of this information As a matter of fact this was the first time a polypeptide hormone was synthesized It is both chemically and physiologically identical with the naturally occurring oxytocin In our clinic we have used a synthetic posterior pituitary oxytocic hormone with excellent results In every respect it compares favorably with the naturally occurring hormone

Uterine Relaxants —There are only two indications for inhibiting uterine contractions the premature onset of labor at a time when the baby has not reached a safe period of viability and rarely for the relief of a contraction ring of the uterus in abnormal labors Until recently there were no drugs developed expressly for these purposes

SYSTEMIC SEDATION —Everyone familiar with the physiology of labor is aware that myometrial activity is impaired by most sedative and general anesthetic agents such as opium derivatives (in large doses) ether and chloroform In average dosage barbiturates have less effect Ether is perhaps the best agent in safe dosage and is probably the most effective means of relaxing constriction rings during labor or in a postpartum uterus strongly contracted by an oxytocic drug There is however, always the danger of serious hemorrhage during the period of relaxation

Sufficient oral fluid intake is desirable to maintain the urinary output at about 2,000 ml daily In the presence of cardiac decompensation, the daily fluid intake should be restricted to 500 ml and the patient digitalized The hypertension is treated by bed rest Sedation should be avoided because of the possibility of masking the signs and symptoms which would indicate the progression of the disease There is no specific treatment for proteinuria Quantitative determinations should be made every 24 hours Catheterized specimens are preferred Urinary protein excretions of 1 to 3 Gm is serious, and if the amount exceeds 3 Gm daily it is of ominous import The patient with mild pre eclampsia can be treated for periods of 7 to 14 days until the state of the cervix warrants induction of labor Cesarean section should be considered if eclampsia is imminent The imminence of eclampsia is indicated by the following signs and symptoms a progressive rise in the blood pressure or a systolic blood pressure which is maintained at a level of 170 or more, proteinuria which is in excess of 3 Gm for 24 hours, a weight gain which is in excess of 100 Gm daily or any sudden increase in weight, the occurrence of head ache, nausea, vomiting, blurring of vision, scotomata, oliguria, the occurrence of hematuria or jaundice, a persistent pulse rate of 120 or more, the appearance of pulmonary edema, cyanosis, or indications of increasing hemoconcentration

Convulsions and coma herald the onset of eclampsia The therapeutic regimen should be directed toward the control of the convulsions, the maintenance of kidney function and the stabilization of the patient so that delivery can be carried out

Eclamptic seizures can be controlled by the use of sedatives such as 6 to 12 ml of 50 per cent magnesium sulfate intramuscularly, 0 25 Gm of Amytal Sodium intra venously every 3 to 6 hours, 3 Gm of chloral hydrate by rectum every 6 to 12 hours with the addition of morphine sulfate if necessary The anuric or oliguric patient presents a difficult problem, for more patients are killed by the overuse of fluids than by neglect Hypertonic glucose solutions (20 to 50 per cent) in limited quantities should be given Dextran or human albumen may be of value Termination of the pregnancy should be accomplished as quickly and as atraumatically as possible

The patient with hypertensive disease may constitute an obstetric emergency at the time of her first prenatal visit Consequently, she should be evaluated at this time If the urea clearance is 50 per cent or more of normal, the Addis count is not markedly abnormal, the 24 hour urinary protein excretion is less than 0 5 Gm, and if there are no significant funduscopic findings and no evidence of cardiac disease, the patient should be advised that the pregnancy may be continued if she is willing to accept the slight but definite risk which its continuation entails Blood pressure, body weight and 24 hour urinary proteins should be determined at each visit If there is an increase in hypertension and proteinuria or if edema or dyspnea develops, hospitalization for study is mandatory Once the decision to continue the pregnancy has been made, every effort is directed to prolong the gestation to at least 32 weeks However, a sudden increase in pro teinuria of 1 Gm or more in 24 hours, sustained increases of 30 mm Hg in systolic blood pressure or 15 mm Hg in the diastolic blood pressure, the progression of retinal pathology, or evidence of renal impairment makes termination of the preg nancy mandatory for both mother and fetus

be related to alterations in the normal steroid metabolism of pregnancy Timely termination of the pregnancy results with few exceptions in complete reversal of the process Residual damage and recurrence of the toxemia in subsequent pregnancies are rare These patients evidence a marked disturbance in their water and electrolyte metabolism An excess weight gain occurring in the second trimester of pregnancy is the first manifestation of these abnormalities As the disease progresses hypertension proteinuria, and edema appear Eclampsia, which has a 7 per cent maternal mortality and a 40 per cent fetal mortality, is the major complication of pre eclampsia

Hypertensive Vascular and Renal Diseases—These diseases in women who become pregnant comprise the second group of toxemias These complications usually manifest themselves in the first trimester of pregnancy The pregnancy may induce an exacerbation of the underlying chronic disease The basic abnormality persists after delivery Marked alterations of water and electrolyte metabolism are unusual in this group Late abortion intrauterine fetal death, severe abruptio placentae occurring in the last trimester of pregnancy and the delivery of premature infants who are markedly underweight for their gestational age are characteristic occurrences

Treatment—The definitive treatment of the toxemias of pregnancy is the termination of the gestation at the most opportune time All other therapeutic measures are palliative Such nonspecific therapy is employed in the mild or moderate forms of the disease with the hope of retarding the abnormal process until delivery of a surviving infant can be reasonably expected A secondary objective of this palliative therapy is to prolong the gestation to the point where delivery through the birth canal can be accomplished The status of the patient with any type of toxemia can deteriorate rapidly Consequently frequent observation and repeated evaluation are of utmost importance in the general management

Although pre eclampsia cannot be prevented eclampsia is preventable in the vast majority of instances provided the patient seeks prenatal care early and follows the advice of her physician Once severe pre eclampsia develops, eclampsia is imminent Hence every patient with moderate pre eclampsia is a potential obstetric emergency and should be hospitalized for evaluation Hospitalization is indicated if one or more of the following signs or symptoms is present a blood pressure of 150/100 mm Hg or more, pretibial or more extensive edema, 24 hour quantitative urinary protein excretion of 1 Gm or more, headache, visual symptoms nausea vomiting and gastric distress or oliguria

When these patients are hospitalized the edema is treated by a low sodium low potassium low chloride diet This regime should not be continued beyond 14 days for prolonged use may lead to serious electrolyte imbalance A diuretic drug may be administered to speed the restoration of a normal fluid and electrolyte balance

Chlorothiazide is most useful and effective in increasing sodium excretion and combating fluid retention in pregnancy It is safe for both mother and fetus and can be administered at any time in the pregnancy under careful supervision In addition to its diuretic effect chlorothiazide is also effective in reducing hypertension in some cases

the threatened loss of a much wanted baby If it is demonstrated that the pregnancy is still viable the pregnancy hormone progesterone, can be administered in moderately large doses It is entirely possible that this key steroid will compensate for the inadequate production of hormones by a poorly developed corpus luteum or by a normal corpus luteum that does not receive enough stimulation by the chorion of a faulty developing conceptus Temporary supplementation of this vital steroid may likewise bridge the gap during the transition from corpus luteum to chorionic hormonal support of the pregnancy

At the first prenatal examination the patient should be instructed to inform her physician if any vaginal bleeding occurs In early pregnancy the causes of the bleeding and its significance are not easy to determine In most instances it is good management to entertain a diagnosis of threatened abortion and treat accordingly

The patient should be put to bed and advised to avoid coitus and catharsis She should save for the doctor s inspection the perineal pads, as well as clots and bits of tissue she may pass A barbiturate or some mild sedative may be indicated in some individuals to allay apprehension If the bleeding diminishes or disappears she can be allowed to resume her normal activities in 48 or 72 hours The prognosis for a pregnancy under these circumstances is good

If she continues to bleed actively or there is a brownish discharge for longer than a week the prognosis of the pregnancy deteriorates The appearance of lower abdominal cramps brought on by uterine contractions may foreshadow the progress of the threatened phase into an inevitable abortion The management of the patient need not change greatly After several days rest in bed she may be up and about with some restriction of her activities Unless the patient develops excessive vaginal bleeding or the process culminates in an incomplete abortion there is no need to terminate the gestation Only continued observation and vaginal examination at intervals will reveal what has happened to the pregnancy Failure of the uterus to grow and a decrease in its size is positive evidence of the death of the conceptus A pregnancy test may provide confirmatory evidence

Abortion is said to be habitual in the woman who has had three consecutively In such a patient an exhaustive study should be made to determine any abnormal factors which may contribute to the abortions Hysterosalpingography is of great value in determining abnormalities of the uterus Some may lend themselves to correction A basal metabolic rate determination may also give valuable information It has been our experience that while hypothyroidism may not exist in the patient hypometabolism may contribute to repeated miscarriages Many patients who have histories of abortions and in whom basal metabolic rates are within the normal range (–10 to –20) benefit from small doses of thyroid extract (30 to 120 mg) This therapy is usually continued to the viability of the fetus

PROGESTERONE —Perhaps the most logical therapy for abortion is the use of progesterone Progesterone deficiency plays an important role in very early pregnancy when abortion may result from inadequate development of the endometrium or from imperfectly developed decidua Later, at about 10 to 12 weeks the transfer of the progesterone secreting function from the corpus luteum to the placenta may be faulty resulting in hormonal deficiency and disturbing normal pregnancy growth and development Previously primarily because of its high cost proges

The termination of the pregnancy can be initiated by the simple rupture of the membranes, provided that the cervical findings suggest that delivery can be anticipated in 24 hours If labor and delivery do not ensue, cesarean section can be performed

Hypertension can be managed by the deep intramuscular injections of 12 ml of 50 per cent magnesium sulfate This is followed by the additional administration of 6 ml every 4 to 6 hours for a maximum amount of approximately 40 ml in 24 hours

The antihypertension drugs have proved to be merely palliative agents It has been the general experience that, although the blood pressure can usually be controlled by these drugs, the underlying disease process is unaltered If visual or cerebral symptoms are present, or if oliguria occurs, a 20 per cent glucose solution in amounts of 1,000 ml is administered in a 40 minute period and repeated every 8 hours if necessary

ABORTION

It has been estimated that about 10 per cent of early pregnancies terminate in spontaneous abortion The incidence increases with age, parity, long periods of infertility, and socioeconomic factors The reduction of fetal loss from abortion is an important medical problem

Causes —Abortions occur because of (1) defective germ plasm, (2) environmental abnormalities sufficiently great to interfere with the normal implantation and development of the conceptus, and (3) inadequate hormonal support In the studies on the etiology of abortion it has not always been possible to uncover all of the factors which may have contributed to the early interruption of a pregnancy Often the factors are interrelated The woman who has a poorly developed endometrium resulting in environmental failure probably also suffers from inadequate hormonal support The interference with the development of the conceptus may result in an insufficient amount of gonadotropic hormone elaborated by the chorionic cells necessary to maintain a healthy corpus luteum

Defective germ plasm, the most important cause of early pregnancy failures, accounts for more than half the spontaneous abortions Hertig and Livingstone have reported that in 489 of 1,000 aborted conceptuses ovular lesions were present It is possible that many abnormal conceptuses are the result of environmental factors which knowledge of the physiology of reproduction could prevent

It has been argued by some that no therapy is indicated for patients who threaten to abort They reason that ovular defects are present in more than 50 per cent of these patients and, obviously, no one wishes to prolong such pregnancies Furthermore in a good many women who threaten to abort the process is inevitable because the damage to the conceptus is sufficiently great to preclude fetal survival Such a defeatist attitude is not consonant with modern dynamic medicine Intelligent therapy can salvage many pregnancies that threaten to abort

Treatment —There is no specific drug therapy for threatened abortion Small doses of phenobarbital may be prescribed for the emotional upset engendered by

it, and the acquired discomfort increases in severity Endometriosis is a common cause In others ovarian neoplasms, adenomyosis of the uterus, inflammatory disease and submucous myomas may be found on examination

Therapy —The patient who develops painful menstruation should have a careful pelvic examination to establish the cause of the discomfort In some women the extent of the pathology may warrant the removal of the uterus In others only an examination under anesthesia or a diagnostic curettage may be sufficiently revealing Drugs for the relief of the discomfort during menstruation are indicated as temporary expedients but should rarely be continued indefinitely

HORMONES —Steroid hormones, estrogens, progestins, and androgens have been used in the treatment of dysmenorrhea The rationale in their use is the suppression of ovulation during the cycle in which they are administered, thereby preventing discomfort

The young woman with primary dysmenorrhea should take 5 mg of diethyl stilbestrol orally each day beginning on the last day of menstruation and continuing for 20 days The subsequent period may be somewhat delayed but it is likely to be painless This regimen may be repeated for 3 or 4 months or even longer, and omitted for a month or two If the dysmenorrhea recurs and is sufficiently severe to interfere with the patient's normal activities, it can be resumed No undesirable sequelae have been reported following such therapy The cessation of treatment is followed by normal ovulatory cycles Eventually the young woman may marry and become pregnant Following the birth of her baby the dysmenorrhea is not likely to return

Similar therapy can be used in the management of secondary amenorrhea induced by endometriosis Long continued estrogen medication to a patient in this condition may keep the disease quiescent, thereby postponing surgical treatment indefinitely

Androgens have also been used to suppress ovulation However, the amounts that need be administered each month may be so large as to induce signs of virilization such as acne hair growth in the masculine pattern, enlargement of the clitoris and even voice changes Their use in dysmenorrhea and endometriosis has no advantage over estrogens and hence they are rarely used today for this condition

MENSTRUAL DISTURBANCES*

General Considerations —The onset of puberty is heralded by the appearance of menstruation The average age of this occurrence is 12½ years However as a result of some neoplasm or endocrinologic derangement, precocious menstruation may occur at a much earlier age or the onset of menses may be delayed until the late teens During the first year or two following the initial episode of bleeding the periods may recur at grossly irregular intervals Maturity and ovulation bring with them a regular menstrual pattern

Irregularities of the menstrual function can occur at any time in life Physiologic amenorrhea occurs in pregnancy and with the menopause Menses may

* [This is also considered in Chapter 31 Ed]

terone was administered in small doses (5 to 25 mg per day) without outstanding success

Since the development of synthetic progesterone, especially long acting progesterone (17-alpha hydroxyprogesterone 17 u caproate), better results have been obtained A single injection of 125 to 250 mg produces effects lasting as long as 2 weeks It is administered intramuscularly in doses of 250 mg once or twice a week In the patient who has had repeated abortions treatment should be begun immediately after the missed menstrual period In patients who have experienced early abortions, it should be continued until 2 weeks after the third missed menstrual period, while in patients who have had late abortions it should be continued to fetal viability Although this therapy is not a panacea for the problem of habitual abortion, it is a logical approach

There has been some discussion as to whether large doses of progesterone or its derivatives given during pregnancy will influence the development of the genital system of the fetus Follow up studies from this clinic and elsewhere have not revealed any aberrations in the development of the reproductive systems of infants whose mothers were treated with progestins during gestation

Diet —An adequate high protein diet supplemented with essential vitamins, particularly A and D, is important in providing optimum metabolism in pregnancy

Reassurance —Emotional support to the patient who is extremely fearful because of a poor obstetrical history has not been sufficiently emphasized in the past

DYSMENORRHEA*

Primary Dysmenorrhea —Primary dysmenorrhea usually begins several years after the onset of the menses with the initiation of ovulation It may be characterized by emotional tension together with cramplike pains in the lower abdomen which may be due to uterine contractions Pelvic examination reveals normal reproductive organs Normal ovarian function is present, for this type of dysmenorrhea is associated with ovulatory periods Suppression of ovulation by estrogens or progesterone may reduce or completely eradicate the menstrual discomfort

Medical treatment should be directed toward psychic and emotional factors which may predispose to the painful periods Young women should be encouraged to participate in exercises of all kinds many lead sedentary lives Good dietary habits, with weight reduction in the young woman who is overweight, should be encouraged Psychotherapy is an extremely valuable adjunct in management and properly used may obviate the need of drugs or hormones There are many combinations of drugs on the market, all of which will give satisfactory results in some cases and fail completely in others These consist mainly of combinations of sedatives, analgesics, and antispasmodics

Secondary Dysmenorrhea —Secondary dysmenorrhea is usually the result of pelvic pathology Characteristically the young woman has been free from discomfort for a number of years after the establishment of the menses She then develops pain of varying degrees associated with the onset of bleeding or preceding

*[Some of these problems are also discussed in detail in Chapter 31 Ed]

docrinal cycle The withdrawal of progesterone would lead to endometrial bleeding in a day or two However, no additional advantages accrue to the patient by the addition of progesterone

Secondary Amenorrhea —The cessation of menstrual periods after they have been established is not an *uncommon occurrence This may be the result of physiologic* changes such as pregnancy and the menopause It can be induced by ovarian failure of varying degrees In some, psychic or emotional factors bring about a limited period of amenorrhea probably as a result of hypothalamic influence on the pituitary gland A major change in the environment may stop the *menses for a short period The marked loss in weight such as occurred in young* women incarcerated in the infamous concentration camps resulted in long periods of amenorrhea It may be brought about by ovarian and adrenal tumors that produce steroid hormones, such as the granulosal neoplasms

TREATMENT —The treatment of secondary amenorrhea depends on its cause The correction of nutritional faults is of prime importance In both overweight and underweight patients, measures to bring the weight to normal are often followed by the return of menstrual periods If the basal metabolic rate is below normal the patient may benefit from moderate doses of thyroid extract Reassurance that menstrual irregularities are rarely of serious import or affect well being may be useful

Excessive and prolonged episodes of uterine bleeding interspersed with periods of amenorrhea *may be a part of the clinical picture of functional uterine bleeding* Mild or moderate degrees of ovarian failure may be evident in the lack of ovulation or its sporadic occurrence A diagnostic curettage may be indicated not only because the endometrial studies will rule out more serious pathology than hyperplasia but also because it will stop the uterine bleeding temporarily Occasionally it is *followed by the recurrence of regular periods*

Hormones Steroid hormone administration is not often indicated in secondary amenorrhea However, if the condition does not improve as a result of the measures that have been instituted and the amenorrhea has lasted for as long as a year, estrogens and progesterone may be tried Where sufficient estrogen is given *to maintain the normal vaginal mucosa as demonstrated* by inspection and cytologic studies and where the reproductive organs appear normal progesterone can also be administered The intramuscular administration of 125 mg of a long acting progesterone twice a week for several weeks should result in uterine bleeding This treatment may be repeated a week or 10 days after the bleeding episode

In these patients there is sufficient estrogen provided by growing follicles to maintain the reproductive organs while progesterone induces progestational changes and on its withdrawal bleeding ensues At the end of 5 or 6 months this regimen can be interrupted to see if natural menses return

If the level of endogenous estrogens has declined so that atrophic changes in the reproductive organs develop, *the administration of* exogenous estrogen is indicated Usually 1 mg of diethylstilbestrol orally, or its equivalent in other estrogenic drugs will result in the recovery of the reproductive organs in a period of several months, following which the daily dose can be reduced to 0 5 mg *This* simple substitution therapy does not influence ovarian function so that it has to

never appear in some young women (primary amenorrhea) Adolescence may be complicated by long episodes of bleeding necessitating therapy Rarely, ovarian tumors with endocrine function, such as the granulosal neoplasms may reinitiate menstrual like episodes of bleeding long after the climacteric Short and long periods of amenorrhea may appear during the active reproductive years of many women (secondary amenorrhea)

Menstruation is an expression of the failure of conception Its character and regularity are influenced primarily by the steroid hormones which control the reproductive function However, physical well being, the state of body nutrition emotional factors, systemic disease, and local pathology, all play important roles The most important part of the management of menstrual irregularities is a pains taking study of each case to determine the cause of the menstrual disorder

Primary Amenorrhea —The failure to establish menstrual periods may be due to the absence of the uterus or complete obstruction to the escape of menstrual blood because of an imperforate hymen The absence of menses may be endocrine in origin The anterior lobe of the pituitary may not produce gonadotropic hormones to stimulate the ovaries, the ovaries may fail to respond to pituitary stimulation or the adrenals may be at fault

No therapy is indicated until the cause of the amenorrhea is established The patient should be subjected to a complete physical examination which should include the visualization of the sella turcica and an x ray study of the urologic tract In the absence of organic causes the endocrinologic investigation should include quantitative urinary assays for gonadotropins and ketosteroids the evaluation of thyroid function and the determination of the genetic sex of the individuals These studies will establish the cause of the primary amenorrhea

Treatment —The treatment of primary amenorrhea ovarian or pituitary in origin, is hormonal substitution In most instances the administration of estrogens induces rapid development of the undifferentiated secondary sex characters the infantile reproductive organs grow to normal adult proportions, and the epiphyses of the long bones close, bringing to a halt continued skeletal growth We administer 1 mg of diethylstilbestrol daily This medication can be continued without interruption indefinitely

These young women may continue to harbor a feeling of inadequacy until it is demonstrated that they can have menstrual periods This is brought about by the withdrawal of estrogens and a breakdown of the endometrium and may last for periods of 3 to 7 days This can be readily accomplished by administering the drug for intervals of 3 or 4 weeks A week or 10 days after the cessation of the medication vaginal bleeding will occur Following the cessation of bleeding the administration of diethylstilbestrol can be resumed Once it has been demonstrated to the patient that she can menstruate if she wishes, she is no longer interested in this useless phenomenon It must be kept in mind that the ovaries are not stimulated by estrogens and that reproduction is impossible It is hoped that it may be possible some day to stimulate such ovaries physiologically, perhaps by pituitary gonadotropic preparations and thereby establish normal ovarian function

A need to substitute for progesterone lack has not been demonstrated One can administer estrogens and progesterone, thereby simulating the normal en

Preparation for the "changing years" should begin long before the onset of t climacteric Mothers should be made to realize that theirs will be a changing ro in their family circles They should be encouraged to develop new interests in t home, in the social group to which they belong, in the church, or in the communit An intelligently occupied woman is less likely to develop emotional problems ar is better able to cope with bodily readjustments brought on by the climacter Such enlightened orientation of the patient may be the most important therapeut tool at the disposal of the physician

HORMONES —Estrogens provide specific therapy for the ovarian failure th brings on the menopause The dosage will vary with the estrogen and the mod of administration When estrogens were first introduced they were ineffecti when administered orally However, today there are numerous estrogenic prepar tions that are effective orally, and the need for parenteral administration shoul arise rarely

The natural climacteric in most women is likely to have a rather slow onse over a period of several years In most patients the administration of estroger can be postponed until menses have ceased It is well to begin with 0 5 mg c diethylstilbestrol every other day and continue this dosage until the menses hav ceased The dose can then be increased to 0 5 mg every day In a few wome this amount may have to be further increased to 1 mg daily for some months i order to control the symptoms completely, following which it should be reduced t 0 5 mg daily We have found that it is best to administer estrogens at bedtime

In a few the onset of therapy with estrogens will cause nausea for a week o 10 days, following which this troublesome symptom disappears It is well to in form the patient that this may occur but that it is of no significance If it persist the hormone can be taken during the day The rare individual may continue to have some transient nausea Natural and synthetic estrogens behave in the same way The cause for this transient nausea is not known

TREATMENT OF SURGICAL MENOPAUSE —The induction of the menopause by the surgical removal of the ovaries or their destruction by irradiation will precipi tate the symptoms of the climacteric within a week or 10 days Experience has taught us that complete substitution of ovarian function in a young woman can be attained by the administration of 1 mg of diethylstilbestrol daily Obviously the woman in the active reproductive years who has lost her ovaries should be placed on 1 mg of diethylstilbestrol orally, or its equivalent in other estrogens within the first week following her operation This dosage will suppress all meno pausal symptoms indefinitely The dose can be cut in half at the end of 6 months and again at the end of a year or two It is important to maintain younger women on a daily dose of 0 5 mg for a longer period than women at or beyond the meno pausal age

DURATION OF TREATMENT —One should remember that estrogens only sup press the menopause The sudden cessation of therapy will be followed by the recurrence of hot flushes in a week or two It is important, therefore that when it is desirable to discontinue medication it should be accomplished by a slow re duction in the amount of the drug administered rather than its sudden with drawal

be continued until ovarian function recovers or, failing that, indefinitely

Irradiation Radiation therapy to the ovaries and the pituitary has been advocated from time to time There is little doubt that some good results have been achieved, but in view of the present increasing concern over the deleterious effects of all radiation such therapy is not warranted for any menstrual disturbance not due to neoplastic disease

THE MENOPAUSE*

General Considerations —The onset of the climacteric is a normal physiologic episode in the lives of most women However, in the minority it may be associated with troublesome symptoms which may tax the physician's armamentarium The slow extinction of ovarian function influences other glands of internal secretion as well as the metabolism of the entire body The necessary readjustments that must be made may be tolerated extremely well by the majority of women but they will cause violent emotional upsets in a few

The period of the menopause frequently coincides with major family and social changes in the lives of many women As the years of the climacteric approach the responsibilities of homemaking become less demanding or completely disappear The children reach maturity and go forth to build their own lives The role of homemaker becomes less exciting and often actual drudgery The family income improves and the husband s business affairs consume more and more of his hours The wife finds that she has more and more time which she occupies by uninteresting and even boring routines She becomes cognizant of many aches and pains real or imaginary

The symptoms and the management of the menopause must be evaluated against the foregoing background Every complaint of a patient from 30 to 60 years old for which the physician has not uncovered an organic cause has been labeled menopausal and often treated as such This approach carries a considerable hazard, for it may overlook serious disease in its incipiency, on the one hand or promote emotional disturbances to the point where they are difficult or impossible to treat, on the other hand There is only one symptom that is pathognomonic of the climacteric, the hot flushes They are vasomotor in origin and are the result of a marked decline in estrogens or their sudden withdrawal Undoubtedly other symptoms occur because of the major hormonal and metabolic changes induced by the lack of estrogens but these are more subtle and more difficult to diagnose

Treatment.—The treatment of the patient who consults a physician because of the change of life must be more comprehensive than the administration of a daily pill if it is to be intelligent treatment The patient should have a complete physical examination to eliminate any organic disease She should have a cytologic study of the cervical and vaginal secretions to uncover cancer sufficiently early to be cured She should be instructed to return for periodic medical examinations Exercise and dietary limitations may be necessary so that she may retain or regain her ideal weight

* [This is also considered in Chapter 31 Ed]

night at bedtime Treatment over a 2 to 4 week period will cure all but the most resistant cases Gentian violet, 1 per cent in glycerin is effective in many cases The vaginal canal is dried with cotton pledgets and then wiped out with the gentian violet solution A tampon lightly saturated with gentian violet may be placed in the vagina and removed in several hours This can be repeated at weekly intervals Nystatin, an antibiotic, in the form of vaginal tablets which can be inserted by an applicator, appears to be an effective agent against moniliasis A tablet can be placed in the vagina each night for a week or 10 days and then every second and third night for 3 or 4 weeks This antibiotic does not disturb the normal bacterial flora

Vaginal Trichomoniasis —This lower genital tract infection is much more difficult to eradicate than is the monilia infection Although many women harbor this protozoan a favorable environment is necessary to produce an acute infection in the vaginal tract with intense burning itching and a profuse purulent discharge The entire lower genital tract is reddened and an abundant bubbly discharge is present The mobile protozoan is easily seen in an unstained hanging drop

There is no specific therapy for this infection Many forms of medication have been recommended, with good results However, in some patients any form of treatment will eradicate the inflammation and in others no therapy is effective It is fairly easy to cure the patient in the acute stage but very difficult if a chronic state exists Recurrences are frequent

An important principle in treatment is to restore the normal biologic environment in the lower genital tract Alpha lactose tablets are inserted in the vagina each night in order to restore the normal pH of the vaginal secretions This medication has been made available in various forms After using these tablets for 4 or 5 nights the patient should douche with vinegar Therapy should be continued for at least 2 months It is important to eradicate foci of infection in the cervix and occasionally in the urethra particularly in the patient who has had a recurrence

In our clinic we have used the following empiric treatment very satisfactorily for many years Negatan, a proprietary drug is a formaldehyde derivative The entire surface of the vagina and portio of the cervix is scrubbed with this preparation and the excess carefully removed Its action is to produce superficial desquamation of the vaginal and portio epithelium The vaginal lumen is then filled with half strength Lassar s paste A tampon is inserted as the speculum is removed to keep the paste from escaping The patient is told to remove the tampon the next day The patient is treated once a week for 5 or 6 weeks and after each of the following three menstrual periods The latter precaution is to diminish the likelihood of recurrences which seem to follow menstruation

Trichomoniasis is difficult to eradicate during pregnancy and the use of alpha lactose tablets will help to control the troublesome itching and discharge

Gonorrheal Vaginitis —Most of the strains of gonococci encountered are susceptible to one of several antibiotics penicillin streptomycin chlortetracycline oxytetracycline, and carbomycin When any of these substances are given over a 4 day period in adequate dosage the infection will be eradicated Local therapy is avoided but the patient should be followed at weekly intervals for urethral

How long should women remain on minimal amounts of estrogens? This question has not yet been answered There are more and more data which support the long-continued administration of estrogens, perhaps into senility Many advantages accrue from small amounts of this hormone Marked atrophy of the vaginal mucosa and postmenopausal vaginitis are prevented Osteoporosis may be delayed or fail to develop Estrogens serve as a tonic to aging tissues because of their influence on the vascular system, and cardiovascular degenerative changes may be delayed or prevented

Dangers —The numerous beneficial effects of the therapeutic use of the estrogens are always clouded by the fear that the treatment may induce neoplasia This is not surprising, for these hormones are the most potent growth promoting factors known However, there are *no* data which definitely implicate estrogens in the development of cancer If there were such a danger, the widespread use of these hormones in small and large amounts for many years should have incriminated them more seriously as carcinogenic agents by this time Emge, a student of this problem for a great many years, has stated that estrogens are not carcinogenic and that at the worst, they may improve the soil for neoplasia in those who are genetically susceptible to neoplastic growth Intelligent treatment with estrogens is probably far less hazardous than treatment with many apparently innocuous drugs that are far less useful

The highly desirable therapeutic benefits of estrogens in the management of the climacteric are not without some hazard They may induce uterine bleeding when the administration of the drug is stopped the dose excessive the amount varied, or even on continued administration Some women are particularly sensitive to estrogens and in them these substances may induce bleeding even when given in small amounts Estrogenic bleeding is of no importance in itself, for it will cease with the withdrawal of the hormone However, bleeding during the climacteric or following its establishment is always a suspicious sign of cancer of the uterus and this serious condition which can be cured in its incipiency, must not go unrecognized Every woman who exhibits vaginal bleeding on estrogenic medication and in whom the bleeding does not stop promptly on discontinuing the hormone should have a careful pelvic examination including a curettage

LOWER GENITAL TRACT INFECTIONS

During the reproductive years most irritations of the vagina are due to one of two organisms *Trichomonas vaginalis*, a protozoan parasite, or *Candida albicans*, a fungus

Moniliasis —Of these two infections moniliasis (candidiasis) is the most easily eliminated This condition is characterized by itching or burning, a profuse irritating discharge cheesy in character Diagnosis should be confirmed by the presence of mycelia in a hanging drop preparation In the patient who is not pregnant one should always suspect diabetes mellitus and examine a urine specimen for reducing substance This organism is present in about 25 per cent of pregnant women There are several agents for the treatment of moniliasis There is available a vaginal gel containing as its active ingredient ricinoleic acid which is very effective This material is placed deep into the vagina by means of an applicator tube each

night at bedtime Treatment over a 2 to 4 week period will cure all but the most resistant cases Gentian violet, 1 per cent in glycerin, is effective in many cases The vaginal canal is dried with cotton pledgets and then wiped out with the gentian violet solution A tampon lightly saturated with gentian violet may be placed in the vagina and removed in several hours This can be repeated at weekly intervals Nystatin, an antibiotic, in the form of vaginal tablets which can be inserted by an applicator, appears to be an effective agent against moniliasis A tablet can be placed in the vagina each night for a week or 10 days, and then every second and third night for 3 or 4 weeks This antibiotic does not disturb the normal bacterial flora

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smears and cultures In immature females the most common cause of vaginitis is the gonococcus The thin mucosa of the vagina at this age makes the individual especially susceptible to this disease

Condylomata Acuminata—These are benign papillomas which occur on the vulva and vagina but rarely on the cervix They are believed to have a viral etiology Frequently they are associated with other vaginal infections such as trichomoniasis

The treatment consists of instituting proper vaginal hygiene The local lesions are treated effectively with 25 per cent podophyllin salve The ointment is applied only to the condylomas and left in place for ½ to 1 hour The medication should then be carefully removed with soap and water Reapplication can be carried out at weekly intervals if necessary In rare cases where the growth is excessively large surgery may be indicated

Postmenopausal or Senile Vaginitis—The atrophy of the external genitalia and the mucosa of the vagina predispose to trauma Trauma invites infection The patient experiences burning or smarting and a serosanguineous discharge On examination the mucosa appears smooth and glistening and reddened and superficial petechiae are visible In some instances it is the burning and smarting at urination that brings the patient to the physician

The treatment is to administer small amounts of estrogens for a period of 6 to 8 weeks The atrophic mucosa rapidly is restored to the normal state and the superimposed infection disappears In women who develop a lower genital tract infection due to trichomoniasis, estrogens are the most important part of the treatment in the postmenopausal period

CHILD SPACING

Child spacing may be desirable because of medical or socioeconomic reasons The physician may wish to instruct the patient concerning the means of preventing pregnancy best suited for the individual s needs

Roman Catholic women who cannot use chemical or mechanical measures to prevent conception may be instructed in the physiologic approach to this problem The normal cyclical changes in the reproductive organs provide for periods of fertility and infertility Abstinence from coitus during the fertile periods decreases the likelihood of pregnancy The basal body temperature is a fairly accurate mirror of these changes The patient can prepare a daily temperature curve by taking her temperature orally immediately upon awakening each morning and recording it promptly The typical temperature graph will highlight the fertile period Suitable graph paper, basal thermometers for easy reading and instructions are available

Contraceptives include occlusive devices such as diaphragms or condoms spermicidal jellies creams capsules and suppositories Spermicidal preparations act as chemical agents Diaphragms serve solely as mechanical obstructions to the migration of spermatozoa upward into the fallopian tubes They likewise provide receptacles for the spermicidal agents Diaphragms should never be used alone The patient who objects to spermicidal agents for personal reasons can use the condom successfully

Spermicidal preparations consist of jellies or creams which provide partial ob struction and in addition contain nontoxic chemical agents which immobilize sperm at relatively low concentrations The viscosity of these preparations should be high enough to prevent leakage but at the same time allow spreading over the cervix and vaginal mucosa

Many compounds have been utilized for this purpose Some of these include 0 33 per cent acetic acid, ricinoleic acid and its derivatives, and many others These agents should not contain greasy substances such as lanolin or petrolatum which tend to cause deterioration of occlusive devices made of rubber

The usual dosage of the creams or jellies is approximately 5 ml Capsules or suppositories are placed in the vagina about 15 minutes before coitus to allow sufficient time for them to melt, spread, and release their active ingredients Re gardless of the measure employed, douches should not be taken within 8 hours following intercourse

Oral Contraceptives—Oral medication which has been rather effective as contraceptive agents has recently been introduced These compounds are the 19 nor steroids, derived from *19* nortestosterone, which is a potent oral progestin The action of these compounds is to inhibit ovulation in both experimental animals and the human female

One of these compounds, norethyndrel, was selected for trial as a contracep tive agent in Puerto Rico Women were given 10 mg of the drug from the fifth to twenty fourth days of the menstrual cycle Withdrawal bleeding occurred within 4 days of cessation of treatment in most cases In 1,279 cycles in which the medication was taken according to directions, not a single pregnancy occurred

Fourteen women who discontinued medication after 1 to 17 cycles became pregnant within 3 months, suggesting that this drug does not impair subsequent fertility These compounds are important in that they demonstrate that control of conception can be achieved with oral medication even though the particular compounds used may not be the ultimate answer

SELECTED REFERENCES

Davis M Edward Natural Child Spacing Garden City N Y , 1954 Hanover House

Davis, M Edward, Adair, Fred L , and Pearl, Sarah Present Status of Oxytocics in Ob stetrics, J A M A 107 261, 1936

Dieckmann Wm J Toxemias of Pregnancy, ed 2 St Louis 1952 The C V Mosby Company

Dieckmann, William J, Harrod, John P, and Monardo Alfred The Treatment of Pre eclamptic Edema With Acetazoleam de (Diamox), Am J Obst & Gynec. 73 789 1957

Eastman Nicholson J Williams Obstetrics ed 11, New York, 1956, Appleton Century Crofts Inc

Emge, Ludwig A Estrogen Imbalance and Uterine Cancer West J Surg 58 490 1950

Fugo, Nicholas W , and Dieckmann William J A Comparison of Oxytocic Drugs in the ... Am J Obst & Gynec 76 141, 1958

... harles C Thomas

... ous Threatened and

... igland J Med 230

797 1944

Jones G Seegar The Management of Endocrine Disorders of Menstruation and Fertility Springfield Ill 1954, Charles C Thomas

P ncus G Rock J , and Garcia C R Effects of Certain 19 Nor Stero ds Upon Repro- ductive Processes, Ann New York Acad Sc 71 479 1958

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TOXICITY —Toxicity of cholinergic drugs is manifested by severe gastrointestinal cramping, profuse sweating generalized or localized paresthesia, shock, bladder pain, salivation and diarrhea. The antidote is atropine The intravenous use of 5 per cent glucose in normal saline may sometimes be necessary

CONTRAINDICATIONS —The cholinergic drugs are contraindicated in (1) patients with myasthenia gravis who are receiving neostigmine, (2) progressive muscular atrophy or bulbar palsy, (3) mechanical intestinal or urinary obstruction, and (4) severe cardiac disease Asthma also makes their use hazardous

Use of Cholinergic Drugs in Nonobstructive Urinary Retention —

POSTOPERATIVE URINARY RETENTION OR POSTTRAUMATIC URINARY RETENTION WITHOUT OBVIOUS SPINAL CORD INVOLVEMENT AND WITHOUT VESICAL OVERFLOW INCONTINENCE —Pilocarpine, 6 to 8 mg, 4 times a day by mouth, may be tried first If pilocarpine fails, Urecholine 10 to 20 mg, 4 times a day, is the next choice If urinary retention persists there should be a cystoscopic examination to eliminate the possibility of either prostatic or urethral obstruction If no obstruction is found, a retention catheter should be used while cholinergic drugs are continued After 4 days the catheter should be removed but the medication continued for an additional 10 days

POSTOPERATIVE OR POSTTRAUMATIC URINARY RETENTION WITH OVERFLOW INCONTINENCE —In this situation the insertion of a retention catheter for 5 days or until the patient is ambulatory for 48 hours if indicated The purpose of the retention catheter is to place the bladder at complete rest and thus augment detrusor compensation by enforced inactivity Pilocarpine 6 to 8 mg 4 times a day by mouth is continued through the catheter period and maintained for 10 days after removal of the catheter If spontaneous urination following removal of the catheter does not occur cystoscopic evaluation is indicated

URINARY RETENTION OF PSYCHIC ORIGIN —In the absence of mechanical bladder neck obstruction as proved by cystoscopy, and with a full bladder treatment consists of intravenous injection of 1 ml of 1 per cent pilocarpine (10 mg) The unpleasant side effects of the pilocarpine as well as the cholinergic action stimulate a distinct desire to urinate normally This therapeutic regimen is never to be used in the presence of cardiac disease

ANTICHOLINERGIC DRUGS

On pages 354 to 356 Almy and Steinberg have described the properties of the anticholinergic drugs as applied to the gastrointestinal tract The factors involved in the urinary tract are essentially identical

A Design for the Use of Anticholinergic Drugs in Urology —In urology the most useful place for these drugs is in the control of a variable degree of vesical spasm which may be occasioned by either pressure (retention catheter or tumor) or irritation (infection tissue congestion)

The bladder neck spasm which is not infrequently associated with a retention catheter may be greatly benefited by the use of tincture hyoscyamus 20 to 30 drops 4 times a day or with methantheline (Banthine), 50 mg 4 times a day In particularly severe instances of vesical spasm the intramuscular use of methantheline, 25 mg every 4 to 6 hours may give relief

THE CHOICE OF DRUGS FOR UROLOGIC DISORDERS

Robert Lich, Jr, M D, M S (Path)

Drugs are used in urologic disorders to combat pain, urosepsis, smooth muscle spasm, to depress or stimulate nerve sensitivity of the urinary tract, and to relieve urinary tract irritation Hormones are also useful in the control of inoperable prostatic cancer, to assist in the problem of infertility, and on occasion to resolve the problem of cryptorchism

The anti infective drugs and agents have made possible unbelievable strides in the treatment of infections while the antispasmodics have had little success If capable of producing smooth muscle paralysis, the latter would interrupt urinary tract function, which would extend rather than correct the patient's plight The antispasmodic must of necessity be limited to serve as an adjunct to specific therapy by hastening subjective relief

In urology symptoms often are the result of the ceaseless rhythmic smooth muscle contractures of hollow viscera which cause distress, the severity is a mirror image of the violence of the irritant It is axiomatic that, except in uncomplicated urologic infection, until the calculus is removed, the obstruction is overcome, or the tumor is removed, medication can serve only as a temporary adjunct

CHOLINERGIC DRUGS

Introduction —The cholinergic drugs are used in urology to stimulate smooth muscle activity of the bladder and, on occasion, of a neurogenically mildly disturbed ureter The cholinergic drugs have their greatest applicability in functional vesical dysfunction and bladder atony resulting from prolonged and recently relieved mechanical urinary tract obstruction Vesical atony may be due to (1) *postoperative or posttraumatic urinary retention*, (2) postprostatectomy bladder atony, or (3) psychic urinary retention

Pharmacologic Considerations —

Mode of Action —Most of the cholinergic drugs now available act as parasympathetic nervous system stimulants by inhibition of cholinesterase, although pilocarpine acts by a different mechanism, stimulating directly Since the parasympathetic nervous system stimulates detrusor and ureteral activity, at least in part, cholinergic drugs may be expected to reproduce this action

General Pharmacologic Considerations —Sodium bicarbonate is the alkali most commonly used in urology However, the acetates, citrates and lactates may also be used since they are converted to carbonates Their effects are those of the chlorides before absorption and those of the carbonates subsequently Oxidation is *virtually complete* so that less than 5 per cent of the acetate, lactate, or citrate is excreted in the urine unchanged

The acetate and citrate *of potassium may* be used to increase alkalinity of the urine and possess the attribute of not neutralizing the gastric juice or disturbing digestion

Sodium lactate, in 1/6 molar concentrations, may be administered intra venously with safety Subcutaneous extravasation will not cause a slough as it may with sodium bicarbonate The lactate solution is also more easily sterilized than the bicarbonate solution Citrates cannot be administered intravenously because they interfere with blood clotting They may also affect the heart adversely by depleting the calcium content of the blood through the formation of an undisso-ciable calcium salt

SODIUM CITRATE —Sodium citrate is the drug of choice when protracted periods of alkalinization are necessary as is the situation in the prevention of uric acid and cystine stones These substances remain in solution in an alkaline urine The *patient must maintain the urine alkaline at all times This must be frequently* checked with Nitrazine paper It is essential that a low calcium diet (no milk or milk products butter excepted) is followed since the alkaline urine may precipitate calcium and the patient formerly troubled with uric acid or cystine stones may find himself confronted with calcium phosphate urolithiasis

SODIUM LACTATE —The 1/6 molar solution administered intravenously is useful in combating the acidosis of uremia or diabetes mellitus It has the advantage of being nontoxic to tissues and possessing a safety factor of wide latitude Sodium bicarbonate on the other hand is toxic to tissues and possesses a markedly small factor of safety so that the patient can easily go from severe acidosis to an equally dangerous alkalemia

Sodium lactate should not be used in severe hepatic disease because its value rests on the action of the liver to alter and make it available as carbonate for the correction of the acidosis

ANTI INFECTIVE DRUGS

The anti infective drugs have played an important role in urologic therapy Since the introduction of sulfanilamide, the list of chemotherapeutic and anti biotic agents has grown This is most fortunate for many of the earlier members have lost their effectiveness Penicillin is a striking example 95 per cent of the strains of *Staphylococcus aureus* were sensitive to penicillin when it was introduced but, within a decade the percentage of sensitivity dropped to less than 10 per cent The drug of choice depends on the specific infection as *well as the clinical setting* Precise diagnosis is therefore, essential to good relief and permanent cure

In the short time that chemotherapeutic and antibiotic agents have been avail able, there have been three phases of therapy first, the narrow spectrum era (e g, penicillin, streptomycin, sulfonamides), second, the broad spectrum era (e g,

The troublesome urinary frequency often found in women, particularly elderly women, without evidence of urinary tract disease is often materially benefited by the use of methantheline, *50 mg*, or *propantheline, 15 to 30 mg every 4 to 6 hours* In this situation the concomitant use of a sedative is materially effective

URINARY ACIDIFIERS

Introduction—Acidification of the urine in urologic disorders has two uses as an adjunct to certain types of urinary antiseptics and as a preventive for urolithiasis in specific instances

Clinical Application and Pharmacologic Considerations—

ANTISEPSIS—Urine acidification is sometimes essential to urinary antisepsis

Methenamine Even today, methenamine has applications in the treatment of urinary infections The value of this drug is a function of the urinary pH, and its optimum antibacterial action depends upon a urine pH of 5 or less

Mandelic Acid Mandelic acid effectiveness depends upon an adequate urine concentration of the drug as well as urinary pH of 5 or less

Penicillin The potency of penicillin in urinary tract infections is enhanced by acidity of the urine

PREVENTION OF STONES—Urine acidification may be useful for the prevention of urinary stones

Sodium Acid Phosphate Sodium acid phosphate is the drug of choice in patients forming calcium containing calculi This drug possesses moderate acidifying properties and reduces urinary calcium excretion, since it depresses serum calcium levels There is some increase in the urinary phosphorus excretion, but this is in the soluble sodium acid phosphate form Sodium acid phosphate will not produce acidosis or bone demineralization *It is used in doses of about 0 6 Gm, 4 times a day* It should be noted that since it must be absorbed in the upper intestinal tract, the enteric coated tablet is valueless Contraindications exist in urea splitting infections since the salt results in more phosphate in the urine in the insoluble magnesium ammonium phosphate form and increases its already excessive deposition

Ammonium Chloride Ammonium chloride is a much more effective acidifier than sodium acid phosphate It is useful as an acidifying agent in conjunction with chemotherapy of the urinary tract, i e, mandelic acid, or penicillin However, ammonium chloride must not be administered over a protracted period since there are certain inherent dangers, i e, bone demineralization, increase of renal excretion of calcium phosphate, and the production of acidosis The dosage is of the order of 0 6 Gm 4 times a day More may be given if the urine pH is not sufficiently depressed

URINARY ALKALINIZERS

Introduction—In urologic problems, drugs affecting alkalinization serve a fourfold purpose (1) to reduce the irritating quality of the urine during periods of bladder inflammation, (2) to prevent precipitation and calculus formation of particular substances, (3) to increase the effectiveness of certain drugs, and (4) to combat acidoses associated with renal failure

isms including pathogens *resistant to other chemotherapeutic* and antibiotic agents The precise mechanism of its action is unknown In the case of urinary tract infections it possesses all the attributes of the antibiotics without their ill effects monilial overgrowth blood dyscrasia, staphylococcus enteritis, or crystalluria Antibacterial concentrations of the drug appear in the urine 30 minutes after ingestion

While it is not common sensitization does occur The symptoms include urticaria, rash and fever The drug should be taken with food to prevent the common side effect of nausea Dosage is 100 mg, 4 times a day

METHENAMINE MANDELATE —Methenamine mandelate (Mandelamine) is a chemical combination of methenamine and mandelic acid Mandelic acid is ineffective unless the urinary pH is less than 5 5 and although the methenamine assists in lowering the urinary pH it may be necessary to supplement with ammonium chloride to obtain the desired urinary acidity Drug fastness rarely develops permitting its use over prolonged periods of time without loss of its effectiveness

Its use is contraindicated in renal failure, since the necessary acidity might cause serious acidosis and is also ill advised in the presence of urea splitting organisms e g *Proteus vulgaris*, which may augment calcium precipitation and calculus formation

Dosage is 4 to 6 Gm per day until the urine is sterile following this the patient may be maintained on half the initial dose

Antibiotics —

PENICILLIN —Penicillin is most effective against gram positive organisms and *thus has only limited value in genitourinary infections*

The procaine salt of crystalline penicillin G in an aqueous suspension is the most commonly used form Penicillin V is a stable in an acid medium and consistent rapid therapeutic blood levels are attained after oral administration Penicillin is usually given in doses of 200 000 to 300 000 daily In unusually severe infections the dosage may be increased to 1 or 2 million units daily *Penicillin* V may be given in doses of 600 000 to 1 200 000 units daily

STREPTOMYCIN —Streptomycin is a narrow spectrum antibiotic which attacks gram negative organisms and the tubercle bacillus Due to its limited scope of action it has been largely replaced by broad spectrum antibiotics in the treatment of infections due to gram negative organisms

DIHYDROSTREPTOMYCIN —Dihydrostreptomycin is used in conjunction with streptomycin in the protracted treatment of tuberculosis because of reduced neurotoxicity

The *dosage regimen in* tuberculosis is about 1 Gm daily for 1 week and 1 Gm twice weekly for at least a year This must be supported by isoniazid 100 mg 3 times a day and paraaminosalicylic acid 12 Gm daily during the year of streptomycin therapy

CYCLOSERINE (SEROMYCIN) —This potentially markedly neurotoxic drug is useful in streptomycin resistant cases of *tuberculosis* and is produced by a strain of *Streptomyces orchidaceus*

Because of its serious neurotoxic properties cycloserine must always be accom

tetracyclines), and now the era of combination therapy The present approach is based not only on the possibility of synergism, but even more important, it represents an attempt to forestall the formation of resistant bacterial strains it is by no means 'shotgun' treatment

The development of sensitivity tests in vitro have proved to be a useful adjunct for specific anti infective medication However, it must be realized that although sensitivity tests are valuable, they are not infallible The therapeutic action and bacterial activity in vitro does not always reflect the in vivo potentialities of the therapy, and clinical judgment still has first place in the treatment of urosepsis

Chemotherapeutic Agents —

SULFONAMIDES —The greatest danger with sulfonamides is precipitation of acetylated sulfonamide in the renal tubule with renal failure This hazard may be minimized by using sulfonamides with little tendency to acetylation and fluid intake which will induce a urine output of at least 2 liters in 24 hours Alkalinization of the urine greatly increases sulfonamide solubility and enhances its therapeutic effect as well

The sulfonamides are effective principally against gram negative organisms which are prevalent in urinary tract infections i e, *Escherichia coli*, *Aerobacter aerogenes* and to a lesser extent *Proteus vulgaris* and *Pseudomonas aeruginosa*

The most common toxic effects are nausea vomiting urticaria rash fever and hematuria Leukopenia or agranulocytosis occur rarely but should be considered during prolonged therapy or even intermittent usage

Sulfisoxazole Gantrisin (sulfisoxazole) does not have a pyrimidine ring as do most sulfonamides in common use and is so soluble at normal urine pH that alkali and large amounts of fluid are not required The usual dosage regimen is 2 Gm followed by 1 Gm every 4 hours Recently, this drug has been made available as its N[1] acetyl derivative Gantrisin Acetyl which is insoluble and tasteless and useful therefore as a pediatric preparation

Sulfisomidine Elkosin (sulfisomidine) has a high solubility and low risk factor The usual dosage is 1 Gm followed by 0 5 Gm every 4 to 6 hours

Sulfamethoxypyridazine Sulfamethoxypyridazine (Kynex, Midicel) is a sulfonamide which is excreted extremely slowly in the urine permitting low dosage at widely spaced intervals Its slow elimination results in low concentration in urine and prevents crystalluria but it is nonetheless effective in urinary tract infections Dosage is 2 Gm initially and 0 5 Gm daily thereafter

Sulfadimethoxine Madribon (sulfadimethoxine) is a low dosage sulfonamide possessing high solubility and excreted as a highly soluble glucuronide Dosage is 1 Gm initially and 0 5 Gm daily in adults

Sulfaethylthiadiazole Sul Spansion (sulfaethylthiadiazole) is a single sulfonamide suspended in a liquid to provide a sustained release of the drug This drug not only has the lowest degree of acetylation of the common sulfonamides but the acetyl derivative is more soluble than the nonacetylated form Dosage is 2 tablespoonfuls initially, followed by 1 tablespoonful every 12 hours (each tablespoonful contains 2 Gm of the drug)

NITROFURANTOIN (FURADANTIN) —This drug possesses a wide range of anti bacterial activity which includes both the gram negative and gram positive organ

CHLORAMPHENICOL (CHLOROMYCETIN) —This is a chemically pure, crystal line broad spectrum antibiotic elaborated by *Streptomyces venezuelae* Cross resist ance to the tetracyclines does not usually extend to chloramphenicol Dosage is 1 to 2 Gm, divided into 4 doses per day

NOVOBIOCIN (ALBAMYCIN, CATHOMYCIN) —This is a broad spectrum antibiotic that is useful in urinary tract infections resistant to other antibiotics It is recom mended in Proteus infections Side reactions are infrequent but do occur in the form of urticaria maculopapular dermatitis, fever, and leukopenia These reac tions subside rapidly upon discontinuation of the antibiotic

Dosage is 1 Gm followed by 250 mg every 6 hours or 500 mg every 12 hours until systemic symptoms are absent for 48 hours

NYSTATIN (MYCOSTATIN) —This antibiotic, derived from cultures of *Strepto myces noursei* is the only one available which suppresses the growth of yeasts fungi, and *Candida albicans* (monilia) It is well tolerated and virtually free from side effects

Dosage is 500,000 to 1,000 000 units 3 times a day and twice as much for systemic moniliasis or severe yeast infections of the urinary tract

POLYMYXIN NEOMYCIN, AND BACITRACIN —The therapeutic spectra of these antibiotics follow Polymyxin, all gram negative bacilli but *Proteus vulgaris* neomy cin in small doses, gram negative organisms and only larger doses gram positive organisms bacitracin, gram positive cocci All present the danger of nephrotoxic ef *fects albuminuria casts and reduced specific gravity of the urine* These findings alone do not however, constitute an indication for drug interruption, since changes tend to reverse after cessation of therapy On the other hand, oliguria (daily out put of less than 500 ml with normal fluid consumption) or progressive azotemia demands immediate discontinuation, otherwise permanent or even fatal lower nephron damage may follow Azotemia without oliguria can occur, and this too demands cessation of the medication These antibiotics should not be used in the face of pre existing intrinsic renal disease

Dosage regimens for these drugs follow Polymyxin 2 to 5 mg per kilogram *per 24 hours neomycin 10 mg per kilogram per 24 hours*, bacitracin 1 000 units per kilogram per 24 hours

A Design for the Use of Drugs in Urosepsis —It must be realized that in spite of modern chemotherapy and antibiotics therapeutic failures may occur and in such instances the patient must have the advantage of a complete urologic and bacteriologic survey Furthermore, the medication must be continued well beyond the period of symptomatology to prevent recurrence Evidence of cure of a urinary tract infection demands that a microscopically or culturally normal urine be obtained on three consecutive weekly examinations after medication has been discontinued The ever rising incidence of serious or even fatal pyelonephritis is attributable to the inadequately treated cystitis of years gone by

If the urine containing pus is acid and gram negative bacilli are observed one can assume the presence of a simple *Escherichia coli* urinary tract infection The sulfonamides and Mandelamine are the drugs of choice since they do not induce resistance to the infecting organism *In the event of a sulfonamide allergy* Mandelamine or one of the tetracyclines may be used

panied by pyridoxine hydrochloride which prevents the neurotoxic manifestations of severe vertigo, mental disturbance, and convulsions

Dosages of 2 Gm daily with 300 mg of pyridoxine hydrochloride are necessary, particularly in seriously ill patients The effective blood level of cycloserine must be maintained at 25 to 30 mcg per milliliter

Erythromycin Propionyl (Ilosone) —This propionyl ester of erythromycin is effective against most gram positive organism and Neisseria and is specifically indicated in staphylococcic infections

The bacterial balance of the intestine is undisturbed after oral administration and therefore staphylococcus enteritis moniliasis, and avitaminosis do not occur Propionyl erythromycin permits much higher effective blood levels with similar dosages than with the erythromycin base

Dosage is 250 mg every 6 hours and in severe infections may be increased to 500 mg every 6 hours

Vancomycin (Vancocin) —This intravenous bactericidal antibiotic is effective against severe staphylococcal and streptococcal infections that are resistant to other antibiotics It does not exhibit any cross reaction with any other known antibiotics or chemotherapeutic agent

This antibiotic should be reserved for desperately ill patients In excessive serum levels it has induced deafness, and in borderline renal disease the presence of casts, albuminuria, and azotemia has been reported

The dosage is 500 mg diluted in 100 to 200 ml of 5 per cent glucose in water or saline and given intravenously over a 30 minute period every 6 hours During the first 10 days 2 Gm is given daily and thereafter 1 Gm daily In children the maximum dosage is 20 mg per pound of body weight

Kanamycin Sulfate (Kantrex) —This bactericidal antibiotic is derived from *Streptomyces kanamyceticus* It is effective against *Staphylococcus aureus* and *albus Escherichia coli, Aerobactor aerogenes, Bacillus proteus* and *Neisseria*

The possible toxic manifestations are (1) renal irritation, seldom seen in children but in adults particularly those with impaired renal function, azotemia may occur with the production of casts, red cells, and albuminuria (these signs of toxicity usually subside upon discontinuation of the drug), (2) eighth nerve dysfunction, in individuals past 50 years of age, manifested by auditory impairment, and (3) skin eruptions occurring infrequently

The dosage is 1 to 2 Gm in 24 hours given intramuscularly in 2 to 4 equally divided doses In children the intramuscular dose is 15 to 30 mg per kilogram in 2 to 4 equally divided doses per 24 hours

Tetracyclines —Recently, tetracycline itself has been added to the original tetracyclines, Aureomycin and Terramycin We now also have tetracycline with sodium metaphosphate and tetracycline phosphate complex The advantages claimed for newer members of the broad spectrum group are more rapid and more complete absorption, absorption higher in the intestinal tract, greatly increased blood levels, and increased urine concentration Cross tolerance is likely to prevail in the case of the tetracyclines, since all exert their antibacterial action through the same mechanism

CHLORAMPHENICOL (CHLOROMYCETIN) —This is a chemically pure, crystalline broad spectrum antibiotic elaborated by *Streptomyces venezuelae* Cross resistance to the tetracyclines does not usually extend to chloramphenicol Dosage is 1 to 2 Gm divided into 4 doses per day

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Should the infection not respond, it may be that it is caused by *Aerobacter aerogenes*, provided the urinary reaction is unchanged The tetracyclines, if not used previously or Furadantin may be used Usually the tetracyclines demonstrate cross resistance If so, an entirely different drug group should be used when changing medication In the event of continued failure and if no urologic complication has been demonstrated chloramphenicol (Chloromycetin), 100 mg, plus propionyl erythromycin (Ilosone), 125 mg, given 4 times a day, are most effective

If pyuria is found in an alkaline urine, the probability of *Proteus vulgaris* infection is most likely In this instance novobiocin (Albamycin, Cathomycin, or Albapenicillin) is usually effective However this organism usually suggests the presence of a urinary tract complication (i e, calculus, residual urine, foreign body, etc) Unless an immediate response is evident, a complete urologic survey is mandatory

Other preparations effective in Proteus infections include chloramphenicol plus sulfonamide Furadantin, and streptomycin

Another increasingly common bacterial infection is that caused by *Pseudomonas aeruginosa* Although this organism is resistant to therapy, it usually responds to one or more of the following streptomycin in combination with Terramycin or Chloromycetin or a sulfonamide, Furadantin in combination with Chloromycetin, or polymyxin Furadantin with Chloromycetin is thought to be more effective than when used alone Polymyxin is a toxic drug and should be reserved for serious infections resistant to other therapies

If cocci including enterococci are found in the urine after it has been thoroughly acidified penicillin is useful or Ilosone with or without sulfonamides may be used regardless of previous acidification of the urine

Summary —As a group, chemotherapeutic agents are more useful than antibiotics in treating urosepsis, since bacterial resistance is less likely to develop and their antibacterial spectrum is broader Combinations of antibiotics, and antibiotics together with chemotherapeutic agents, offer additional protection against therapeutic failure due to bacterial mutation and unrecognized secondary invaders

ANALGESICS FOR GENITOURINARY PAIN

Introduction —The narcotics are virtually the only analgesics useful in urologic disorders associated with pain due to smooth muscle spasm, i e, urolithiasis, infection, tumor penetration, etc

The Several Drugs —

Morphine —Morphine is the most useful drug in the treatment of urinary tract colic Dosage must be adequate, in a healthy robust male with ureteral colic this is 30 mg followed by 15 mg every 3 or 4 hours

There is the danger of respiratory failure However, since pain causes respiratory stimulation as long as it persists, pain is an effective antidote

Demerol —Demerol (meperidine) is a less effective analgesic than morphine, but it has less tendency to induce smooth muscle spasm Dosage is of the order of 100 or 150 mg intramuscularly, repeated every 3 hours in 100 mg doses In the doses above, the danger of respiratory depression is less than with morphine

RATIONAL BASIS FOR NEW CHEMOTHERAPEUTIC AND ANTIBIOTIC DRUGS

The production of new chemotherapeutic and antibiotic agents will continue and valuable products will evolve However, *as in the past, not all* additions will be useful or even desirable The factors to be considered in evaluating a new product are (1) effective bacterial spectrum, (2) effective antibacterial blood level, and (3) toxicity

It is important to realize that the actual blood level of any drug or antibiotic is not necessarily indicative of its effectiveness, since charts showing blood levels are often most useful in sales promotion Factors of toxicity must be carefully evaluated and investigated, since the manufacturer is careful to point out the hazards but not infrequently these factors have not attained their full evaluation when the product is released

Drug or antibiotic combinations have certain advantages, but the combined product may be designed to catch the physician's eye rather than his judgment *Generally the physician can prescribe his own combination which will be much* more effective in the particular situation considered

In short as the new antibiotic and chemical agents are released, it is the physician's responsibility to consider each on its merits and proved capabilities rather than to adopt a spectacular graph which may reflect only an enthusiastic conclusion based upon studies under the most optimal conditions

SELECTED REFERENCES

Cholinergic Drugs

Henderson, V E, and Roepke, M H The Role of Acetylcholine in Bladder Contractile Mechanisms and in Parasympathetic Ganglia, J Pharmacol & Exper Therap *51* 97, 1934
Scott M Retention of Urine of Neurogenic Origin Relief by Subcutaneous Injection of Pilocarpine Hydrochloride, J Urol 47 58?, 1947

Alkalinizers

Finland M Murray R Harris, H W, Killam, L and Meads M Development of Streptomycin Resistance During Treatment, J A M A 132 16 1946
Lich R Jr Kidneys Fluids and Electrolytes J Kentucky M A 53 219 1955

Acidifiers

Keefer C S Evaluation of Antibiotic Therapy, Postgrad Med 9 101 1951
Lich R Jr Some Basic Therapeutic Concepts in Urosepsis M Times 85 22 1957
Lich R Jr Some Practical Considerations Concerning Fluid and *Electrolyte Therapy,* South M J 43 542, 1950
Prien E L Pathogenesis and Medical Management of Urolithiasis Bull New England M Center 13 102 1951
Yeaw, R C The Effect of pH on the Growth of Bacteria in the Urine J Urol 44 689 1941

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Phemerol and mercurials have been recommended for use as bactericidal teriostatic agents However, sterility will not be maintained unless the sealed

Boric acid retards the growth of fungi but does not kill pathogenic Many of the wetting agents such as Zephiran do not inhibit the growth o ganisms some of the agents are incompatible with many of the alkaloi The combination of polymyxin B and Zephiran possesses a broad spectrun rapidly bactericidal

Stability of Solutions —The stability has been thought to be related hydrogen ion capacity Some activity may have to be sacrificed to maint bility

Choice of Vehicle —In order to facilitate the passage of medic through the cornea hydrophilic compounds should be administered in anh vehicles and lipid soluble compounds in aqueous solution

Ointment Vehicles —The most popular ointment vehicle is a petr base containing 25 per cent hydrous wool fat or lanolin Ointments are im because they remain in contact with tissue longer than do aqueous preparati

Methods of Application of Ointments and Solutions —The tip of squeezed for application should not touch the diseased surface especially t de sac Ointment may be applied to the lid margin with a sterile cotton cator Most ointments applied to the lids will not induce damage to th junctiva

Drops for the conjunctiva are usually instilled in the lower cul de sac may also be applied by having the patient look down while the upper lid vated The dropper or the tip of a plastic bottle should never touch the e dropper or bottle should not be used for several patients without sterili Since the annoyance may be considerable, gelatin discs or wafers (lamella instillation into the cul de sac are no longer in widespread use

Drugs may be applied directly to the conjunctiva lids or corneal surf dipping a bit of cotton wrapped tightly on a metal or wooden applicator th been dipped into the agent The excess of the drug is allowed to flow off pr ocular application While it is a safe procedure application directly to the junctiva is rarely practiced

Methods To Enhance Intraocular Penetration of Locally Ap Drugs —*Subconjunctival injections* are usually made in eyes previously anesth locally The injection may however induce subconjunctival hemorrhage *C packs* are performed by placing some wisps of cotton in the cul de sac of the l anesthetized eye and soaking these cotton fibers with the selected solution cotton pack must not rub on the lower or upper poles of the cornea, since co abrasion might lead to corneal ulcer *Corneal baths* by means of various cup not widely employed

Heat may be applied to the eye in dry form by means of an infrared l Moist heat may be applied with hot compresses generally as hot as can be enc on the back of the hand and placed on the closed lids They should be rem d ... for at least twenty minutes every second hou

THE CHOICE OF DRUGS FOR OPHTHALMIC USE

Irving H. Leopold, M D.

ADMINISTRATION METHODS FOR OCULAR PHARMACOLOGIC AGENTS

All the routes of administration are employed in ophthalmology oral topical, intradermal subcutaneous intramuscular, intravenous, and inhalation Most common, however, is local administration in the form of drops ointment, cotton packs, corneal baths and subconjunctival injections Iontophoresis or electrophoresis is sometimes used to increase the penetration of some drugs Drugs may also be injected directly into the anterior or vitreous chamber, or retrobulbarly

Local Ophthalmic Preparations –The ideal ophthalmic solution should be free of microorganisms easily sterilized, nonirritating, physiologically active, stable, of low toxicity and surface tension of high wetting power, compatible with other agents, and inexpensive

The hydrogen ion concentration of a solution necessary to maintain its best physiologic activity and stability to reduce irritability, and to facilitate corneal penetration may be controlled and maintained by buffering Tears have a high buffering capacity A very satisfactory buffer is a mixture of anhydrous dry sodium phosphate

Detergents as Ophthalmic Vehicles – The penetration of most agents through the cornea can be facilitated by lowering of surface tension or by wetting agents While it has been pointed out that detergents such as aerosol and Duponol have some toxic features, Phemerol and benzalkonium (Zephiran) have excellent wetting power, low toxicity, and also have bacteriostatic and bactericidal properties Despite some drawbacks benzalkonium has received widest use It has been suggested that all ophthalmic solutions should be isotonic with tears Most solutions are hypertonic, but, owing to the protection of the tears and conjunctival fluid, do not produce irritation or damage unless repeatedly instilled or used in large amounts

Solutions can be sterilized by mechanical filtration, heat, and the use of chemicals Boric acid, chlorbutanol, derivatives of benzylic acid, benzalkonium chloride,

The Several Miotics —

Physostigmine (Eserine) —This drug should be dispensed in a small well enclosed container which has been protected from light and stored in a cool place Instillations of ointment will blur visual acuity and therefore are usually reserved for use at retiring Solutions of physostigmine salicylate are irritating to most eyes and decomposition further increases the irritation Boric acid added to the solution will reduce the tendency to decomposition Preparations in an oily base are less irritating Solutions of physostigmine are used as a miotic and are instilled frequently enough to control intraocular pressure A strong eserine solution may have to be employed to counteract the effect of cycloplegics such as homatropine or atropine

Pilocarpine —Pilocarpine solutions are stable in air and do not deteriorate on standing Whereas the miosis of eserine might persist for 2 days, that of pilocarpine usually persists for less than 1 day, but pilocarpine is generally less irritating and is the best tolerated of all the miotics to date

Neostigmine (Prostigmin) —Neostigmine is an anticholinesterase agent which unites with this enzyme in reversible fashion The bromide is soluble in water and alcohol and stable in solution It is often used alternatingly with Mecholyl chloride

Methacholine (Mecholyl) —Methacholine solutions lose potency on standing A solution of 10 or 20 per cent concentration should be renewed every 2 or 3 weeks it should be refrigerated

Carbachol (Carcholin, Doryl) —Carbachol is more stable than Mecholyl Because it is poorly absorbed through the cornea, it must be used with a wetting agent or in an anhydrous vehicle such as petrolatum It can be used to replace pilocarpine when sensitivity makes that desirable

Bethanechol (Urecholine) —Bethanechol is probably as effective as carbachol, both should be used with caution in asthmatic patients Urecholine may be used in 1 or 2 per cent concentration with a wetting agent

Isoflurophate (DFP, Floropryl) —This drug is a powerful miotic with more prolonged effect than either physostigmine or Prostigmin It is used in 0 01 to 0 1 per cent concentration It must be made up in an anhydrous vehicle In strong solution it may produce a precipitous rise in intraocular pressure, particularly in eyes with narrow angles

Mintacol (Bayer 600) —Mintacol lowers intraocular pressure in concentrations from 1 5 000 to 1 10,000 It is water soluble but less potent than DFP

Phospholine Iodide (Echothiophate, 217-MI) —This drug in concentrations as dilute as 0 2 per cent aqueous solution is stable at room temperature for at least 1 month It possesses all the disadvantages of other strong miotics but is extremely effective in the control of chronic wide angle glaucoma, aphakic glaucoma and congenital glaucoma

Adrenergic Blocking Agents —These agents induce mild miosis by relaxation of the dilator of the pupil

Dibenamine is administered intravenously, the pupil becomes small, the conjunctival blood vessels dilate, and in normal human eyes there may be a slight fall in intraocular pressure Administered by slow drip in saline, it is effective in acute

Moist *cold* can also act as an analgesic since it induces vasoconstricti... sage may sometimes be employed to facilitate filtration after a glaucoma ...

THE SEVERAL DRUGS

Miotics

Clinical Applications of Miotics—Miotics are primarily used in the th... of glaucoma but have recently been applied in accommodative esotropia or co... gent strabismus They prevent the iris from moving into the surgical incision ... intraocular surgery The anticholinesterase variety of miotics is used for the tr... ment of pediculosis of the lashes

Disadvantages of Miotics—Miotics may produce ciliary spasm browac... headache false myopia and undesirable rises in intraocular pressure Most mioti... have action of only short duration Patients may become hypersensitive to th... agent and many eyes develop resistance Miotics may be absorbed systemically after instillation in the eye and may produce undesirable parasympathomimetic stimulation Asthma due to bronchial constriction may result

Mode of Action of Miotics—Decreased resistance to outflow due to miotics can occur either by an increase in the number of draining channels which are open or by a slight increase in the diameter of each channel Through their dilating effect on the small intraocular vessels miotics may reduce the osmotic effective ness of the aqueous humor i e vasodilation tends to lower the intraocular osmotic pressure with the consequent diminished tendency to draw fluid from the blood stream

Table 49 Drugs Acting on Parasympathetic System (Parasympathomimetics)

Drugs acting on effector cells so as to mimic action of acetylcholine or the so-called neu rohumoral transmitters	Inhibitors of the enzyme cholinesterase which normally hydrolyzes the neurohumoral transmitting agent acetylcholine (the action of the locally produced acetylcholine is there fore markedly prolonged)
Pilocarpine	Physostigmine (eserine)
Carbachol (Doryl)	Neostigmine (Prostigmin)
Furtrethonium (Furmethide)	Isoflurophate (Floropryl)
Methacholine (Mecholyl Cl)	Mintacol (Bayer 600)
	Phospholine iodide (217 MI Echothiophate)
	Demecarium Br (BC 48) (Humorsol)

Despite different pharmacologic activities and sites of action the influence of ... miotics on intraocular pressure appears to be similar Some miotics work ...idedly better when a wetting agent is added to the vehicle e g carbachol ...ryl) Isoflurophate (Floropryl) is stable only in an anhydrous solvent Echo...phate (phospholine iodide) is practically as potent but stable in water solution ...veral weeks at room temperature Mintacol (Bayer 600) is also more stable ...er solution than is isoflurophate

... is advisable for the physician to have several miotics since each can serve ... purposes and switching may sometimes be necessary when hypers... ...n reactions occur

employed in aphakic glaumoca if the weaker or the less congestive ones fail uveitis the stronger miotics are usually avoided

STRABISMUS —In accommodative strabismus, central innervational stimula to the ciliary muscle is reduced by stimulating the ciliary muscle by local administration, and the associated convergence mechanism is not called into pla strong fashion The long acting miotics such as dilute preparations of DFI echothiophate are utilized

Mydriatics and Cycloplegics

Purpose of Mydriasis —Mydriasis allows adequate examination of the fun Usually the weaker mydriatic agents are employed These are also used to di the pupil, to reduce the incidence of posterior synechia formation in uveitis, as a provocative test in eyes with narrow angles to determine whether dilatatio the pupil will lead to closure of the angle and a rise in intraocular pressure

The stronger mydriatics, which also act on the ciliary body and put ciliary muscle at rest, are known as *cycloplegics* They are employed so that fractive errors can be measured accurately and to bring about rest of the pupi the dilated position and of the ciliary body in iritis, cyclitis, and diffuse uve The stronger cycloplegics are not used for examination of the fundus as th action lasts too long

Table 50 Classification of Autonomic Drugs Used in Ophthalmology—Cont

Drugs acting as sympathomimetic agents	Drugs producing varying degrees of parasy pathetic paralysis
Amphetamine (Benzedrine)	Atropine
Cocaine	Homatropine
Epinephrine	Eucatropine (Euphthalmine)
Ephedrine	Scopolamine
Hydroxyamphetamine (Paredrine)	Hyoscyamine
Naphazoline (Privine)	Dibutoline (Dibuline)
Phenylephrine (Neo-Synephrine)	Methantheline (Banthine)
Procaine	Oxyphenonium (Antrenyl)
	Atropine methylnitrate (Eumydrin)
	Cyclopentolate (Cyclogyl)
	Lachesine (E 3)
	Ganglionic blocking agents
	Tetraethylammonium chloride (TEA, Etamon)
	Pentamethonium
	Hexamethonium
	Pentolinium (Ansolysen)

The Several Mydriatics —Atropine, in 1 to 3 per cent concentrations, produc the maximum of pupillary dilatation in approximately 2 hours It is a very pote cycloplegic and mydriatic of long lasting action It should be avoided in patien with narrow angles The action of hyoscyamine is the same as that of atropin Scopolamine is most commonly employed in a strength of 0 25 per cent Ho matropine has its maximum effect on the pupil and ciliary muscle within 1 to 2 hour its action persists for approximately 24 hours Lachesine (E 3) is well tolerated an produces satisfactory mydriasis in 30 minutes Its cycloplegic effect is variabl

glaucoma Some cases of narrow angle glaucoma respond by a fall in intraocular pressure The drug should not be used in patients with cardiovascular disorders

Tolazoline (Priscoline) causes a slight rise in intraocular pressure when injected subconjunctivally With parenteral administration no significant influence on intraocular pressure has been observed It has more effect on glaucomatous than on normal eyes it has been suggested for a provocative test for early glaucoma when administered subconjunctivally

Clinical Applications —

ACUTE GLAUCOMA —Acute glaucoma is both a medical and a surgical problem Medical treatment aims at opening the angle of the anterior chamber Attempts to lower intraocular pressure by medical means should be made for at least 12 hours before performing emergency surgery During the attack the comfort of the patient may require the administration of morphine hypertonic solutions and also dibenamine applied intravenously as well as carbonic anhydrase inhibitors The effect of oral administration will be less rapid

During the acute rise in intraocular pressure not associated with congestion the weaker miotics should be employed When the eye is congested or the pressure is high combinations such as 2 per cent pilocarpine and 0 25 to 0 5 per cent physostigmine can be used Anticholinesterase agents other than eserine and prostigmine should be avoided in acute or angle closure glaucoma It should be remembered that the use of large amounts and concentrated solutions of miotics may be followed by such systemic symptoms as nausea diarrhea muscular twitching and urinary urgency During the acute phases miotics must also be instilled into the unaffected eye as it may be subject to an attack of angle closure glaucoma

CHRONIC SIMPLE GLAUCOMA —

Criteria of Control and Selection of Miotic The treatment is largely medical as long as the intraocular pressure is controlled and there is no evidence of visual deterioration as indicated by changes in the visual fields If the pressure tends to e on the high side of normal and there is no change in the visual fields the pa ent is usually carried on medical therapy

Administration The frequency and concentration required for instillation de nds on the severity of the glaucoma Usually the miotic is instilled on awaken in the morning at noon evening and on retiring If the pressure is controlled demonstrated by checking the visual fields the patient may continue on this men indefinitely It is important that the pressure be checked at different s during the day as well as at regular intervals throughout the year

The mainstay of therapy for chronic glaucoma is pilocarpine The newer ics are to be employed as adjuvants to replace pilocarpine if necessary or in ion to it DFP and phospholine iodide (echothiophate) are the most potent cs available and have prolonged action but should not be used in eyes with w angles lest they cause a rise in intraocular pressure

FLECTION OF MIOTIC IN SECONDARY GLAUCOMAS —Miotics are particularly ve in aphakic glaucoma and in the late stages of glaucoma secondary to quiet and may be helpful in the glaucoma associated with hemorrhage in the r chamber or that due to exfoliation of the lens capsule or pigmentary deposi n the angle The stronger miotics such as DFP and phospholine may be

4 times a day is warranted Neo Synephrine can also be applied as a pack in the cul de sac Atropine can be instilled into the pack at the same time These agents can be administered subconjunctivally to break synechia or to obtain wider dilatation of the pupil Sympathomimetic agents administered in this fashion may bring about cardiovascular effects apprehension, tension and even hypertension

Analgesics and Anesthetics

Analgesics and anesthetics are used pre and postoperatively Morphine morphine derivatives and substitutes are frequently used but codeine is commonly used for the relief of postoperative pain Acetylsalicylic acid is frequently employed for relief of mild pain, often in combination with codeine

Local Anesthetics —Cocaine was employed in local ocular anesthesia for many years At present tetracaine (Pontocaine) is the most widely used local anesthetic The 2 per cent solution may be employed for the removal of corneal sutures or for the removal of a foreign body from the cornea Very little conjunctival irritation follows instillation into the cul de sac and it does not appear to influence the intraocular pressure or accommodation

Benoxinate (Dorsacaine), in a 0 4 per cent solution produces rapid anesthesia with minimal irritation by local instillation It is short acting and is satisfactory for the removal of foreign bodies and if repeatedly instilled for corneal surgery

Butacaine (Butyn) has a rapid onset of action and long duration It does not affect the pupil when locally applied into the cul de sac and is less damaging to the cornea than is cocaine The high degree of hypersensitivity it produces limits its usefulness Dibucaine (Nupercaine) is a potent but very toxic local anesthetic Piperocaine (Metycaine) is used as a 2 per cent solution of 4 per cent ophthalmic ointment Phenacaine (holocaine), as a 1 per cent solution is slightly irritating smarts when instilled but produces very little hypersensitivity Proparacaine (Ophthaine) is rapid in action does not damage the corneal epithelium and seems to be less irritating than most of the other agents

Retrobulbar Anesthesia —The drug used most for retrobulbar block in ophthalmology is procaine in 2 to 4 per cent solution Lidocaine (Xylocaine) may be a trifle more potent than procaine but is also more toxic than procaine The addition of a vasoconstrictor prolongs their activity

More rapid anesthesia is induced by the additional use of hyaluronidase Following hyaluronidase and procaine infiltration behind the globe, the intraocular pressure as well as the retro orbital pressure is reduced considerably This is believed to reduce loss of vitreous in cataract extraction

For local anesthetic purposes drugs such as tetracaine (Pontocaine) and phenacaine (holocaine) may be used interchangeably For infiltrating anesthesia procaine is still the drug of choice although lidocaine may be substituted if necessary

Hypotensive Ocular Drugs

Treatment of Glaucoma —Treatment really began with the use of eserine and pilocarpine the mainstays of medical antiglaucoma therapy In addition to miotics which are applied locally to the globe there are agents which lower intraocular

Cyclopentolate (Cyclogyl), in a 0.5 to 5 per cent concentration, produces dilatati of the pupil and cycloplegia within 45 minutes. Methantheline (Banthine), er ployed as an ointment in a 4 per cent concentration or as a 2 per cent solution, pr duces effective mydriasis and very little cycloplegia within about 30 minutes. Pr vine, in a solution of 0.05 to 0.1 per cent, produces marked vasoconstriction anc mydriasis. Veritol (oxyphenyl isopropylmethylamine), in a 1 to 5 per cent concen tration produces rapid mydriasis with a slight enlargement of the palpebral fissure and changes the intraocular pressure very slightly. Benzedrine, an effective my driatic, acts in about 30 minutes but irritates the conjunctiva. Cocaine, usually employed in 2 or 4 per cent concentration, produces dilatation of the pupil and vasoconstriction. It may cause some roughening of the corneal epithelium.

UNTOWARD EFFECTS.—A number of these agents have undesirable features. Atropine, scopolamine and all of the cycloplegics may produce flushing of the face and may induce fever. Patients develop hypersensitivity to local instilla tion of these agents. One of the disadvantages of refraction with a cycloplegic is that the patient is inconvenienced during its effect. Cyclogyl has been popular in recent years since its cycloplegic effect wears off rather quickly.

Miotic agents can be instilled to overcome the cycloplegic or mydriatic effect of drugs. With strong mydriatics one must employ a stronger miotic. Phospholine (echothiophate) and DFP are used to counteract strong cycloplegics such as atropine or scopolamine. Instillations have to be made repeatedly. It is difficult to neutralize precisely the effect of one drug with the other.

CLINICAL VALUE OF SYMPATHOMIMETIC AGENTS.—Most of the sympathomimetic agents are employed to dilate the pupil or to blanch the conjunctival vessels, and some of them will lower intraocular pressure in glaucomatous eyes. They should not be used in eyes with narrow angles. Neo Synephrine in 10 per cent concentration is frequently used in the treatment of wide angle glaucoma and in glaucoma secondary to uveitis to dilate the pupil, which helps to put the eye at rest, prevents synechia and also tends to lower intraocular pressure. These agents can be used in combination with cycloplegics to bring about greater dilatation of the pupil to help break synechia and to prevent the pupil from being closed by nflammatory membranes. Cycloplegics as well as mydriatics may provoke a rise n intraocular pressure in eyes with narrow angles. The physician should check ntraocular pressure and also if possible determine the state of the angle of the nterior chamber prior to the instillation of these agents. Otherwise, it is safer use the weaker mydriatics for examination of the fundus.

Privine and others of these agents are used as provocative tests for glaucoma ticularly of the angle closure variety.

Design for the Use of Mydriatic Agents.—When Cyclogyl is used, the pa 's eyes are ready for refraction within 45 to 50 minutes. Its action can be come by instillation of 1 per cent pilocarpine. The effect of the drug wears pontaneously within 12 to 18 hours. Following instillation of homatropine, mination can be done after 1 hour. However, its cycloplegic and mydriatic persists longer than that of 5 per cent Cyclogyl.

or dilatation of a pupil in an eye with uveitis, atropine should be instilled times a day. If necessary, the addition of 10 per cent Neo Synephrine 3 or

or in temporary lowering of intraocular pressure so that miotics can become more effective

SUMMARY —The carbonic anhydrase inhibitors have proved to be of definite value in the therapy of glaucoma Patients with chronic glaucoma have been maintained over a 3 year period with their use along with that of miotics On the other hand in angle closure types of glaucoma the prolonged use of Diamox may allow peripheral synechia to develop so that more serious intraocular surgery will be needed when the pressure is no longer controlled

The carbonic anhydrase inhibitors also have side effects weakness central nervous system disturbances drowsiness numbness loss of appetite, diarrhea tingling in the fingers, toes, and around the lips and nose renal calculi and colic skin eruptions blood dyscrasias and perhaps even liver damage

The problem of the control of intraocular pressure may be approached locally and/or systemically More attention is now paid to combined medication Obstruction to the aqueous outflow, the basic defect in glaucoma as a rule can be relieved medically by the use of miotics in chronic simple or wide angle glaucoma and with surgery in uncomplicated angle closure types i e miotics and iridectomy

Anti inflammatory Agents

Agents which retard inflammation in the eyes include those which oppose infection as well as those with specific anti inflammatory activity, e g steroids and analgesics

There are a number of ocular inflammations for which the etiology cannot be determined This is particularly true of uveitis Here nonspecific measures such as the use of foreign protein steroids antihistaminics, and alicylates must be employed For some corneal diseases for which the etiology cannot be established or when the etiology is due to a virus for which there is no specific agent therapy with cauterants has been tried

Antibiotics administered systemically do not all penetrate into the eye equally well Chloramphenicol penetrates better than most of them Isoniazid also penetrates readily The sulfonamides differ in their ability to penetrate There are variations in the penetration of locally applied drugs depending on the water solubility the vehicle the state of the corneal epithelium the tonicity of the solution and whether or not a wetting agent is included

Steroids —Steroid therapy has definite value in a wide variety of ocular conditions They control inflammation and exudation produced by allergies trauma and bacteria until other forces overcome the inflammation Administration is local as well as systemic only ACTH is restricted to systemic administration

Undesirable side effects occur with all the steroids Fortunately most eye conditions can be treated locally and do not require prolonged systemic use although a few of them such as sympathetic ophthalmia and chronic uveitis may Dosage must be adequate and carefully graded Careful observation of all patients is essential Virus diseases of the cornea such as herpes simplex keratitis may progress during steroid therapy though the patient i comfortable

Other Anti inflammatory Agents —Acetylsalicylic acid as well as the salts of salicylic acid are used by mouth as antipyretics and analgesics in a variety of

pressure when administered systemically They include those which lower systemic blood pressure, those which affect the central nervous system, carbonic anhydrase inhibitors such as Diamox, hypertonic solutions adrenergic blocking agents such as dibenamine, hormones such as pituitrin, enzymes such as hyaluronidase, and curariform agents

Adrenergic blocking agents and ganglionic blocking agents, such as hexamethonium, are thought to decrease the rate of formation of intraocular fluids Chlorpromazine may reduce intraocular pressure by reducing the inflow of intraocular fluid General anesthetics, for example, ether, have no specific effect on intraocular pressure, but thiopental and other central nervous system depressants, frequently employed as preoperative medication may induce a marked drop in intraocular pressure in eyes with chronic simple glaucoma Local anesthetics such as 2 per cent procaine hydrochloride and 1 per cent lidocaine hydrochloride cause a decrease in intraocular pressure of at least 5 mm Hg in most instances after retrobulbar injection

Hormones —An increase in intraocular pressure during menstruation and lowering of intraocular pressure with progesterone in glaucoma have been reported These effects are of short duration In patients in whom glaucoma may be secondary to an intraocular inflammation the pressures may be lowered as a result of the quieting of the inflammatory process by ACTH Pituitrin injected subconjunctivally has been shown to lower intraocular pressure

Enzymes —The injection of hyaluronidase was found by Barany to cause a decrease of approximately 50 per cent in the resistance to outflow in excised animal eyes However, the addition of hyaluronidase to the aqueous humor in vivo or the injection of hyaluronidase outside the eye has not been observed to lower intraocular pressure

Curariform Agents —These agents may lower intraocular pressure by diminishing the tone of the extraocular muscles

Diuretics —In glaucoma, irrespective of its cause, there is usually an accompanying local decompensation and water logging It was found that a number of diuretics reduce intraocular pressure Salyrgan with theophylline produces a very slight drop in intraocular pressure, a reduction in resistance to outflow, and a slight reduction of inflow Peak effects are seen 24 hours after administration

Carbonic Anhydrase Inhibitors —Inhibitors such as Diamox and dichlorphenamide (Daranide) produce a drop in intraocular pressure Patients who were formerly controlled on 250 mg of Diamox 4 times a day were controlled on 100 mg of Daranide (dichlorphenamide) 4 times a day, or 200 mg 3 times a day Cardrase (ethoxzolamide) and Neptazane (methazolamide) are other effective carbonic anhydrase inhibitors [No significant difference among the four has been established Ed]

Central Nervous System Depressants —Because of the profound influence of emotion on intraocular pressure, there is interest in the tranquilizing agents in glaucoma Chlorpromazine (Thorazine) and reserpine, among others, have been shown to lower intraocular pressure but there is no great practical value to most of them Perhaps their chief value lies in pre- and postoperative care of patients

*Table 51 Prophylaxis of Intraocular Infection**

Agent	Dosage	Time of Administration	
		Preoperative	Postoperative
Chloramphenicol	*Initial*		
	3 Gm orally	3 hr	
	Maintenance		
	1 Gm every 6 hr		48 hr
	Initial		
Penicillin†	1,000 000 units—I M or I V	1 hr	
Streptomycin	2 Gm I M or I V	1 hr	
	Maintenance		
Penicillin	1,000 000 units every 8 hr		48 hr
Streptomycin	1 Gm every 8 hr		48 hr
Tetracycline	*Initial*		
	3 Gm orally	3 hr (or earlier)	
	Maintenance		
	1 Gm every 6 hr		48 hr
Gantrisin or sulfonamide combinations	*Initial*		
	2 Gm orally		
	Maintenance		
	1 Gm every 4 hr		48 hr
	Subconjunctival at time of surgery		
Erythromycin	2 5 5 mg/0.5 ml		
or bacitracin	10 000 units/0 5 ml		
or novobiocin	15 000 units/0 5 ml		
+			
polymyxin B	50 000 units/0 5 ml		

*From Leopold, I H Recent Advances in Ocular Therapy, New York J Med 56 2807 1956

†Benemid 2 Gm orally with initial dose of penicillin ½ Gm every 6 hours for maintenance

INFECTIONS OF THE LIDS, CONJUNCTIVA, CORNEA, AND LACRIMAL APPARATUS

Marginal Blepharitis.—Inflammations of the lid margin may be due to infections, allergy or degenerative diseases Cases of seborrheic origin may respond to local applications directed against seborrhea, anointing the lid margins carefully with Selsun or various antifungal dyes such as brilliant green, or mechanical cleansing followed by the application of a bland ointment Staphylococcic blepharitis may respond to sulfonamide preparations or to various ointment bases containing gram positive effective antibiotics Cases of allergic origin will respond to steroid applications A number of conditions will not respond to local therapy with chemotherapeutic agents, these include localized lupus erythematosus, xeroderma pigmentosum, and others

Conjunctivitis —This requires specific diagnosis and therapy Solutions should be instilled every hour or two during the day and ointments applied for the night Any discharge should be irrigated from the eye with an innocuous collyrium prior to instillation

Corneal Infections —Corneal inflammations usually require large doses of antibiotics systemically as well as locally Subconjunctival injection and iontophoresis are satisfactory local methods of obtaining adequate concentration

ocular conditions and sometimes rectally in infants Phenylbutazone (Butaz administered orally is used primarily as an antipyretic and analgesic, but it a to help in rheumatoid conditions and in such ocular diseases as uveitis The many undesirable side effects

ORGANIC GOLD COMPOUNDS —Aurothioglucose may be employed in uv particularly in those forms related to rheumatoid arthritis It appears to some value in nondisseminated lupus erythematosus The initial intramusc dose of 25 mg a week is gradually increased until a total of 1 000 mg has b given

Gold sodium thiosulfate is given by intravenous injections starting with dose of 5 mg and is cautiously increased Gold therapy may cause severe u toward reactions and opinion is divided as to whether the risk is worth taking

ORGANIC MERCURY COMPOUNDS —Merbromin (Mercurochrome) is a non irritating moderately active antibacterial agent It is incompatible with acid acid salts heavy metals hydrogen peroxide and most alkaloids and local anes thetics The aqueous alcohol acetone solution called merbromin surgical solution is more rapid in action than the aqueous solution The drug penetrates signifi cantly only into dying or dead tissue Solutions of nitromersol (Metaphen) should be prepared as needed as they tend to precipitate upon standing It is a local antibacterial agent is relatively nonirritating and is employed particularly in ophthalmology for disinfection of the skin Thimerosal (Merthiolate) is usually used in a 0 1 per cent solution and as such it is a relatively nontoxic skin disin fectant Like other mercurial antiseptics it cannot be relied upon to produce complete sterilization Spores are particularly resistant

Ammoniated mercury is prepared in ophthalmic ointment and is used on the eyelids as an antiseptic It is employed for crab louse infestation of the lashes and l d margins for impetigo psoriasis and ringworm Yellow mercuric oxide oint ment is rarely used in ophthalmology since in effective doses it is extremely irri tating to the eye Mercury bichloride is applied as an antibacterial ointment in the form of a mercury bichloride ophthalmic ointment mixed with water and white petrolatum

ZINC COMPOUNDS —Zinc sulfate may be employed as an eyewash for the treatment of conjunctivitis caused by Morax Axenfeld bacillus It may also be applied to the skin of the lids as a 4 per cent solution for treatment of acne ivy poison lupus erythematosus and impetigo Zinc oxide is usually employed around the lids in eczema impetigo ringworm pruritus and psoriasis Zinc is chiefly used for its astringent and antiseptic properties

BORIC ACID —Boric acid solution is used chiefly as an irrigant and for appli cation to the cul de sac and cornea A 2 2 per cent solution is thought to be isotonic with tear fluid Serious poisoning can result from oral ingestion of as little as 5 Gm

IODINE —Strong iodine solutions are used for the cauterization of corneal ulcers particularly those due to herpes simplex No excess iodine should touch the adjacent cornea This is followed by instillation of 4 per cent cocaine solution after which the eye is flushed to remove any excess iodine

Isoniazid may be used effectively locally on external tuberculous infection of the eye but it is predominantly employed systemically along with streptomycin

Nitrofurazone (Furacin) is used in 1 500 *solution or ointment for the treatment* of mixed infection of the lids and conjunctiva For preoperative preparation of the skin and for irrigation of the eye, benzalkonium is an all purpose local antibacterial agent with a *detergent, keratolytic and emulsifying action* In concentrations of 1 2 000 or stronger, it may produce reparable corneal infiltrations and irritation which clear when the drug is stopped

The Use of Steroids

Cortisone —Cortisone is now used for acute inflammatory processes in the posterior segment and for anterior ocular inflammations which do not respond to local therapy For ophthalmic patients oral administration is satisfactory The usual dose is 300 mg the first day in divided doses 200 mg the second day and 100 mg thereafter Therapy in reduced dosage should be continued until all danger has subsided When the drug is cut down gradually the physician must be on guard against recurrences For topical therapy suspensions and ointments of cortisone may be employed The following routine is suggested Cortisone acetate suspension in drops of 0 5 per cent or 2 5 per cent should be used every hour and ointment of 1 5 per cent should be applied at night because it may produce blurring If this fails, subconjunctival injection of 0 5 ml of a 2 5 per cent suspension of cortisone acetate every 3 days should be used If this fails oral and parenteral therapy may be tried

Hydrocortisone —Oral administration is started at 100 mg a day in divided dosage and is reduced with clinical response Hydrocortisone may also be given intravenously

Corticotropin (ACTH) —ACTH is without effect locally nor can it be given by mouth It may be administered intramuscularly Initial dosage varies from 80 to 100 mg per day divided into 4 doses given at 6 hour intervals These intervals should be continued and doses reduced or increased according to response Long acting preparations may be given at 12 hour intervals For intravenous therapy 25 mg a day of ACTH may be dissolved in glucose in water and given as an intravenous drip over a period of 8 hours once daily This method seems to be from 8 to 12 times as effective as the intramuscular route After the ocular tissues have responded one may switch to intramuscular ACTH Some cases which fail to respond to cortisone hydrocortisone and to other steroids may respond to ACTH

Prednisone and Prednisolone —These may be given orally in doses of 30 to 40 mg daily until therapeutic response (2 weeks maximum) followed by the minimal amount required to maintain the remission Intramuscular predni one acetate *25 mg per ml is not often indicated* in ocular disease suspensions are used at 0 5 to 2 5 per cent

Others —Methylprednisolone (Medrol) triamcinolone (Aristocort) and dex*amethasone (Decadron Deronil)*, are now also available for systemic administration They are effective at a lower dosage schedule than is required for prednisone or prednisolone

Table 52 Therapy of Intraocular Infection*

Agent	Method of Therapy	Antibiotic	Dosage	Freque
Penicillin-streptomycin combination†	Subconjunctival injection	Penicillin + Streptomycin	1,000,000 units/1 ml of 1 1,000 Adrenalin or water 100,000 µg/1 ml of 1 1,000 Adrenalin or water	Inject u 0 5 ml for 2 d
			(If overwhelming infection)	
	Intravitreal injection	Penicillin +	5 000 units/0 05 ml	Once
		Streptomycin	1,000 units/0 5 ml followed by subconjunctival injection as above	
			(Also give same drugs systemically)	
	Systemic therapy	Penicillin§	1,000,000 units—initially I V 1,000,000 units I M	Every 6
		Streptomycin	1 Gm—initially—I V ½ Gm I M	Every 8
Chloramphenicol‡	Systemic	Chloramphenicol	3 Gm stat 1 Gm	Every 6
Tetracycline	Systemic	Tetracycline	3 Gm stat 1 Gm	Every 6
Other antibiotics	Subconjunctival injection	Polymyxin B +	50,000 units/0 5 ml H_2O with 1 1,000 Adrenalin	
		Erythromycin or	2 5-5 mg/0 5 ml H_2O	
		Novobiocin or	15,000 units/0 5 ml H_2O	
		Bacitracin	10,000 units/0 5 ml H_2O	
	Systemic	Gantrisin + any of above subconjunctival injections	2 Gm stat 1 Gm	Every 4

*From Leopold I H Recent Advances in Ocular Therapy, New York J Me 2808, 1956

†Therapy to be instituted if prophylactic chloramphenicol therapy has been unsu ful

‡To be used if prophylactic penicillin and streptomycin therapy have been unsucc

§Benemid 2 Gm orally with initial dose of penicillin, ½ Gm every 6 hours for tenance

Lacrimal Infections — Inflammations of the lacrimal gland are rare ev mumps the lacrimal gland may not be affected For tuberculosis and sy treatment is the same as for these diseases in other parts of the body In in mations involving the canthus with Streptothrix, removal of concretions mec cally usually suffices

Infections of the lacrimal sac can be cleared temporarily with antibiot chemotherapeutic agents Unless the obstruction, which usually occurs belo lacrimal sac, is removed the infection will recur Antibiotics may be admini systemically or may be injected into the sac Injection into the sac, if it i tended is extremely painful and should be avoided if possible Once the tion is overcome, the obstruction may be removed by surgical procedures Tables 51 and 52 for concentrations used in subconjunctival administration

dermatitis of the lids, allergic blepharitis, insect bites, and in the prophylactic therapy of virus keratitis

Antazoline (Antistine) is not as irritating as many other locally applied antihistaminics *Diphenhydramine (Benadryl)* produces considerable sedation Promethazine (Phenergan) produces effective sedation and is also used for its antiemetic action

When systemically administered antihistaminics may produce blurred vision weakness of accommodation and corneal edema

The Use of Antibiotics

With the advent of antibiotics and chemotherapeutic agents there has been a great reduction in visual loss due to infection For successful antibiotic therapy it is essential that the organism causing the infection be identified, that it be sensitive to the antibiotic chosen, and that an effective concentration of the chosen agent reaches the site of infection If an infection fails to respond within 48 or at the most 72 hours a switch to other medication is indicated Sensitization to penicillin following local instillation may prevent the use of penicillin for a more serious systemic infection at a later date Ophthalmologists therefore tend to use such antibiotics as bacitracin, neomycin, polymyxin and gramicidin which are not likely to be used systemically They may be administered locally in the form of solutions with or without a detergent The penetration of antibiotics into the eye may be enhanced by iontophoresis, subconjunctival injection retrobulbar injection and injection directly into the chambers of the eye

If antibiotic therapy fails, considerable destruction of normal tissue may have taken place and visual loss may continue Corneal abscesses may become sterile under treatment but, because of the tissue destruction associated with the infectious process the cornea may perforate

Prophylaxis and Therapy of Intraocular Infections—In the potentially infected wound, e g , penetrating foreign body injury it is advisable to treat the eye as though it were infected A broad spectrum antibiotic or a combination of antibiotics should be used In intraocular surgery some ophthalmologists are reluctant to use prophylactic anti infective drugs Here the ophthalmologist must weigh the advantages to the patient against the risks involved No one questions the use of chemotherapeutic agents in the patently infected case The major problem is the use of antibiotics in clean and contaminated cases

Wounds inflicted on the eye with the keratome or knife and scissors may be contaminated In spite of all precautions, infection is reported in approximately 0 5 per cent of most large series of intraocular surgical cases With the exception of the hemolytic streptococcus the causal organisms are frequently resistant to the commonly employed antibiotics The fact that antibiotics are inefficient in the presence of dead tissues makes it unlikely that routine chemoprophylaxis will further reduce this low incidence of postoperative infections in clean surgical cases

The combination of penicillin and streptomycin provides a broad antibacterial spectrum which in adequate concentration should be bactericidal against many organisms that are secondary invaders in the eye Chloramphenicol may be used

Ointments may cause visual blurring and are preferred for night use Sub conjunctivally 0 5 ml of a 2 5 per cent suspension of prednisone or prednisolone acetate may be injected under Tenon's capsule for severe diseases of the anterior segment Prednisolone phosphate may be used in 0 5 to 2 5 per cent solution for drops or for subconjunctival injection Fludrocortisone, methylprednisolone, triamcinolone, and dexamethasone are available for topical use

Topical therapy makes for high local concentrations without systemic effects The drugs absorbed into the anterior segment are of benefit in iritis aphakic toxic reactions, and in other conditions of the anterior uveal tract They are of no value for inflammation of the posterior segment

Clinical Applications—The steroids are useful in the following conditions

Seborrheic blepharitis marginal blepharitis due to contact dermatitis and drug reactions

Conjunctivitis due to staphylococcic toxin sensitivity, phlyctenular conjunctivitis, allergic blepharoconjunctivitis, chemical and thermal burns

Inflammation of the cornea and sclera marginal ulcer of cornea, interstitial keratitis (syphilitic or nonspecific) superficial punctate keratitis atopic keratoconjunctivitis, keratitis disciformis with close observation for recurrence of dendritic ulceration recurrent corneal erosions, scleritis, episcleritis

Inflammation of the uveal tract (nongranulomatous and granulomatous) iritis, iridocyclitis or chorioretinitis (acute or chronic)

Miscellaneous conditions herpes zoster ophthalmicus neovascularization of conjunctiva and cornea, pseudotumor of the orbit, glaucomatocyclitic crisis, glaucoma secondary to uveitis, postoperative corneal edema following keratoplasty

Untoward Effects in the Eye—Except for the possibility of combinations with acetylsalicylic acid and vitamin C which may allow smaller doses of steroids to bring about the desired effect, combinations of steroids with other drugs should be avoided General contraindications and the careful observation required in the use of adrenocorticosteroids are familiar to all physicians

Local use of steroids may delay the absorption of blood from the anterior chamber and also of cortical material after extracapsular extraction of the lens or traumatic injury of the lens The prolonged use of a combination of steroids with antibiotics may contribute to an increased number of fungous infections in the cornea

Local use of steroids may be followed by complications such as the onset or advance of herpetic keratitis Make certain that there is no herpes keratitis and *watch the patient closely so that this can be detected as soon as it develops* If, in addition the physician is alert to the possibility of a fungus keratitis developing in an already diseased eye, it may be safe to try these agents in red eyes before an etiologic diagnosis is made

The Use of Antihistamines

Clinical Use—Antihistamines are most effective in allergic conjunctivitis, urticaria of the lids, and reactions to drugs They may also be helpful in contact

THE CHOICE OF DRUGS FOR OTOLARYNGOLOGIC DISORDERS

William H. Saunders, M D.

THE CHOICE OF ANTIBIOTICS

In otolaryngology most failures *with antibiotics and chemotherapeutic agents* are due to the fact that the following criteria are not followed (1) The microorganism must be sensitive to the drug, (2) the drug must be given in effective dosage, (3) the infected area must have a good blood supply, and (4) there must be adequate drainage of pus

The systemic use of these drugs is usually more effective than topical administration Topical application also tends to sensitize the patient to the drug *When the infecting organism has been identified, the choice of antibiotic or* chemotherapeutic agent is usually the same as in any other infection The reader is therefore referred to Chapters 7, 8, and 9 on the choice of antimicrobial agents Only the basic problems of their application to otolaryngologic infections will be considered here

THE SEVERAL OTOLARYNGOLOGIC DISEASES

Diseases of the Ear

External Otitis —The chief symptom of acute external otitis is pain and that of chronic external otitis is itching In the normal ear canal only *Staphylococcus albus* and diphtheroids are present, neither is pathogenic In external otitis (acute or chronic) the streptococcal, *Staphylococcus aureus*, proteus, and pyocyaneus organisms predominate Often the infection is mixed Most of these infections can be controlled by a combination of bacitracin, neomycin, and polymyxin B Albamycin (novobiocin) is the only common systemic antibiotic that now seems to be effective against most of the strains of staphylococci

Acute External Otitis —*Unfortunately, even though in vitro tests are used* to determine the best drug, for several reasons not all patients recover with local treatment First, failure to clean the ear canal carefully before applying medication leaves masses of soggy debris of macerated epithelium in which bacteria continue to grow Second, the ear canal may be so swollen that the medication (used as

despite the small danger of blood dyscrasia, on the basis of its broad antibacterial spectrum and great penetration into the ocular tissues when systemically administered. Tetracycline penetrates into the intraocular tissues and fluid when used in massive doses intravenously and orally, but there are many resistant strains of *Staphylococcus aureus*. Novobiocin penetrates poorly into the intraocular tissues when systemically administered, but it will penetrate following subconjunctival injection.

Pyrimethamine (Daraprim) is the treatment of choice for uveitis of toxoplasmic origin. It is not always possible to establish the definite diagnosis, but the drug can be used with sulfadiazine or alone for therapeutic trial. If depression of erythropoiesis occurs the drug may be stopped.

Because of the frequency of resistance of *Staph. aureus* to penicillin, the use of erythromycin combined with Gantrisin has been recommended for prophylaxis against ocular infections. Erythromycin penetrates the blood aqueous barrier, particularly when given intravenously or intramuscularly in maximal doses. Intraocular infections due to fungi have increased in incidence. Amphotericin B has helped some of these.

The Contaminated Case.—Because the ocular tissues are so close to the otopharynx, it should be considered a contaminated field. Primary emphasis is on the preoperative reduction of the bacterial flora with appropriate antibiotics. Such a course of action, however, will not guarantee complete protection. The use of antibiotics in traumatic open wounds of the eye should begin at once and continue through the operative period and for 72 hours thereafter. Then the ocular appearance will determine whether or not the antibiotic should be continued.

SELECTED REFERENCES

Dunphy, E. B.: Radioactive Isotopes in Ophthalmology, Bull. New York Acad. Med. 33: 310, 1957.

Gordon, D. M.: Prednisone and Prednisolone in Ocular Diseases, Am. J. Ophth. 41: 593, 1956.

Kratka, W. H.: Isoniazid in Ocular Tuberculosis, A. M. A. Arch. Ophth. 54: 330, 1955.

Leopold, I. H.: Pharmacology and Toxicology, A. M. A. Arch. Ophth. 48: 163, 1952.

Leopold, I. H.: Antibiotics in Ophthalmology, Tr. Am. Acad. Ophth. 58: 821, 1954.

Leopold, I. [illegible]

Leopold, I. [illegible]

Leopold, I. [illegible]

Leopold, I. [illegible] Tr. Am. Acad. Ophth. 60: 210, 1956.

Leopold, I. H. [illegible] G., and McDonald, P. R.: Local [illegible] Ophth. 34: 361, 1951.

[illegible] Steroids in the Eye, A. M. A. Arch. [illegible]

[illegible] ine on Intraocular Pressure in Experimental Animals, Am. J. Ophth. 41: 318, 1956.

Paul, S. D., and Leopold, I. H.: The Effect of Tranquilizing and Ganglionic Blocking Agents on Intraocular Pressure, Am. J. Ophth. 42: 752, 1956.

Complications of Acute and Chronic Otitis Media.—Although such complications as meningitis, brain abscess, epidural abscess, and labyrinthitis are rare, they still occur When they do, heroic antibiotic therapy is essential Massive doses of penicillin are used in meningitis Chloromycetin and sulfadiazine are also given if indicated

ACUTE MASTOIDITIS—Acute mastoiditis results from acute otitis media If myringotomy is done for acute otitis media and if the proper antibiotic is given long enough and in sufficient dosage, acute mastoiditis rarely develops In the now rare case of acute mastoiditis, antibiotics administered in high dosage and for a prolonged period (several weeks) usually cures A few still require simple mastoidectomy to remove granulation tissue and diseased bone

CHRONIC OTITIS MEDIA AND CHRONIC MASTOIDITIS—In chronic otitis media or chronic mastoiditis (usually the two co exist) the problem often consists of one part low grade infection and two parts obstruction The normal mastoid is a honeycomb of air cells and normal drainage is obstructed The bone infection granulation tissue, and cholesteatoma require surgical removal Systemically and topically administered antibiotics are of little use

Diseases of the Nose and Paranasal Sinuses

The nose and paranasal sinuses have cilia that beat constantly and as a result topical medications are carried away with the mucous blanket Therefore, topical anti infective medication is not very effective in the nose or paranasal sinuses

Acute Sinusitis—Obstruction that makes for poor drainage is common in sinusitis and as a result, antibiotics are less effective than was originally hoped The treatment of uncomplicated acute sinusitis is almost always medical no hard and fast rule can be given however Manipulative or surgical procedures are contraindicated because they tend to spread infection or even cause osteomyelitis Patients with fever and pain may require antibiotics, others may not

Acute Rhinitis—Acute rhinitis is almost always due to the common cold a viral disease Here antibiotics are not effective

Chronic Sinusitis—As in chronic mastoiditis so in chronic sinusitis antibiotics are ineffective Multiple small abscesses form in the mucosa of the sinuses and mucoceles or polyps obstruct drainage Some patients with a subacute form of sinusitis respond well to irrigations of normal saline Treatment of chronic sinusitis is surgical

Other Acute Nasal Conditions—Septal abscess and acute bacterial rhinitis respond well to antibiotic therapy

Diseases of the Pharynx

The blood supply is good and usually there is no obstruction to drainage All that is needed is the correct drug given long enough in adequate dosage

Acute Tonsillitis—This condition responds readily to most of the broad spectrum antibiotics Repeated infections may, however, also indicate a tonsillectomy Peritonsillar abscess (quinsy) is another indication for tonsillectomy

Adenoiditis and Nasopharyngitis—The adenoid often causes disease of the ear and nasal obstruction When these are produced by an adenoid which is not

drops) cannot get far enough along the canal. A third reason for failure i
spread of infection to neighboring tissues. Lymphadenopathy and periauri
edema indicate that topical medication will not do and that systemic antib
is needed. In most patients with a severe acute external otitis it is always
to use antibiotics or sulfonamide drugs systemically in addition to local medicat
In some patients, particularly those without fever or great pain, it is not alw
necessary or even advisable to use topical antibiotics in the ear canal. Occasiona
however, a wick saturated with Burow's solution, half strength, works well as t
sole therapeutic agent.

Chronic External Otitis.—In chronic external otitis without acute exace
bation the chief symptom is itching and the patient greatly enjoys having his e
cleaned. It is extremely important to remove every bit of debris from the ea
canal and surface of the eardrum. Depending upon the condition of the epithelium
ointments or ear drops should be used. On scaly dry epithelium, ointments work
better; liquid preparations are better for oozing macerated epithelium. When
infection is present the proper antibiotic should be used in an ointment. When
infection is minimal a mild exfoliating and antipruritic ointment such as that
below is satisfactory.

		Gm. or ml.
R	Phenol	1.0
	Salicylic Acid	1.0
	Precipitated Sulfur	1.0
	Petrolatum	30.0
S	Use once daily for 1 or 2 weeks or even indefinitely to control itching and scaling.	

Patients often do not apply ointments properly. Usually they use a commercially prepared cotton applicator that is too thick for the ear canal. They should make their own applicators with a tuft on the end by winding cotton about a toothpick.

For the wet type of chronic external otitis, ear drops of half strength Burow's solution should be used first. When the skin has become dry an ointment should be used.

Otitis Media.—Acute otitis media is caused by an infection passing up the eustachian tube. Often it is more important to re-establish the function of the tube than to treat with antibiotics. In children and in some adults hyperplastic adenoid tissue is the most common cause of obstruction and adenoidectomy is the best treatment. When there is an abscess in the middle ear, pus must be released and myringotomy may be more important than drugs. Hearing is spared by releasing pus.

Topically applied antibiotics are of little or no use in acute otitis media. If the eardrum is not ruptured the drops cannot reach the middle ear, whereas if the eardrum is perforated the draining pus keeps the drops out. Systemically administered antibiotics or sulfonamides are indicated in most instances. A culture of the pus is often not possible because the pus is behind an intact eardrum. If pus is obtained through myringotomy, it is still necessary to begin treatment before the infecting organism is identified. Penicillin, erythromycin, and sulfonamides are good drugs to use at this time.

Cresatin —Used as drops or on a cotton wick, Cresatin is a good fungicide Care must be taken, however, not to cause additional irritation The drug may also cause some burning in patients with acute external otitis Treatment is usually continued several days or a week

Nystatin (Mycostatin) —This drug is effective in ear drops and ointments

Drugs Used in the Oral Cavity

The treatment of monilial and other fungous growths of the oral cavity is an old problem to the otolaryngologist Two per cent aqueous gentian violet applied topically helps many but not all patients Nystatin, 2 or 3 tablets (500 000 units each), 3 times daily, helps more Many cases of stomatitis are produced by antibiotics (particularly as lozenges) which deplete the normal bacterial flora of the mouth and permit overgrowth of yeasts

NOSE AND THROAT SPRAYS AND PAINTS

In the days before antibiotics, infections of the pharynx were commonly treated with sprays or paints" The physician, pressed to do something for his uncomfortable patient, applied medications directly to the inflamed pharynx None of the drugs he used was curative Nevertheless, some of these medications did provide symptomatic relief and even now, many patients still ask to have their throats painted' Still useful because of its great symptomatic benefit, and also probably of some curative value, is a stream of hot water directed at the posterior pharyngeal wall A quart of hot unmedicated water is used in an enema or douche can two feet above the patient s head Water runs in strikes the tonsillar area or posterior pharyngeal wall and runs out into a basin Gargling is much less effective

CORTICOSTEROIDS

The corticosteroids are probably of less value in otolaryngology than in most other medical specialties, but there are several otolaryngologic conditions in which these drugs are useful and sometimes essential

External Otitis —Sometimes good results in acute external otitis are obtained with an ointment containing hydrocortisone Edema and inflammation are reduced and in some instances pain is relieved faster than would be expected otherwise Fortunately no local or systemic reactions result from the use of hydrocortisone

When used in chronic external otitis hydrocortisone may seem to give a good result at first but often the relief is short lived and the itching returns Preparations containing 1 to 2 5 per cent hydrocortisone in hydrophilic ointment are available with and without antibiotics

Acute Allergic Rhinitis —Although not the drug of choice in the treatment of the average patient with acute allergic rhinitis corticosteroids administered systemically sometimes control symptoms controlled by usual methods The topical intranasal use of hydrocortisone was originally expected to provide great relief in hay fever but these high hopes did not materialize

infected but is hyperplastic, adenoidectomy is the only treatment adenoid becomes infected, systemic antibiotic therapy is indicated

Diseases of the Oral Cavity

The usual throat lozenge, with its relatively low concentration of does no good, but it may do harm by permitting overgrowth with yeast moniliasis develops

Diseases of the Larynx and Trachea

Inflammatory Laryngitis—Most patients have acute laryngitis as part upper respiratory infection However, laryngitis may be the only abnorma dition

VOICE REST—Patients with inflammation of the larynx get well faster if rest the larynx Complete voice rest implies that the patient neither speaks whispers, partial voice rest, that he may whisper softly when necessary

STEAM INHALATION—Inhalation of water vapor (steam from a teakettl does much to relieve cough and to restore moisture to a larynx which may be di and feel scratchy The water need not be medicated Failure to obtain relief b the use of steam may be due to the use of a small steamer in a large room If a room steamer is to be effective, droplets of water should form on the walls

ANTITUSSIVES—The patient with laryngitis does better if he can be kept from coughing The best cough suppressive is codeine, which should be given every 2 hours

SMOKING—Although smoking is absolutely contraindicated many patients who complain bitterly about laryngitis refuse to give it up even for a short time

THROAT SPRAY—In the era before antibiotics physicians anxious to do some thing for their patients often prescribed various topical medications for relief of laryngitis None did much good Laryngitis is not only a superficial mucosal inflammation but also a submucosal one There is some justification for antibiotic sprays or aerosol preparations but in general when used at all these should be used only as adjuncts to systemic antibiotic therapy

SULFONAMIDES

The sulfonamides may be destined for a 'comeback' as more and more organisms develop resistance to the antibiotics The new sulfonamides can be given at long intervals and hence are most convenient In addition they are cheaper than antibiotics

FUNGICIDAL DRUGS

Drugs Used in the Ear

In temperate climates, fungous infections of the external auditory canal are common Most external otitis is due to bacteria but occasionally both acute chronic external otitis are caused by fungi Treatment with fungicidal dru sually successful if the ear canal is carefully cleansed of accumulated uamated epithelium.

drug is used as is necessary Only a hand spray, not a pressure spray, should be used to obtain topical anesthesia in the throat Since only the drug which adheres to the mucosa is effective, the patient should expectorate the excess material In the nose a spray can be used, or the anesthetic can be applied on a cotton pledget, excess anesthetic solution should not drip into the throat

Cocaine —Cocaine is still the best and most effective topical anesthetic There has been a great deal written about accidents associated with this drug, but when examined carefully such reports are often found to be misleading Used correctly, cocaine solution, 5 to 10 per cent, is safe for mucous membranes of the nose and throat

Tetracaine (Pontocaine) —Pontocaine is as potent a topical anesthetic as cocaine and at least as toxic

Lidocaine (Xylocaine) —Much modern bronchoscopy is done under topical Xylocaine anesthesia The drug is relatively less toxic than cocaine and Pontocaine, but it is also weaker Xylocaine viscous is useful in patients with ulcerated painful lesions in the mouth, pharynx, or esophagus, in which a moderately potent topical anesthetic is needed

Dyclonine (Dyclone) —Dyclone is another good topical anesthetic for oral lesions It can be used in a mouthwash and expectorated or, better, applied to cotton and left in place The drug may also be swallowed in amounts up to one ounce to provide anesthesia of the esophagus preliminary to esophagoscopy

Topical Anesthesia of the Eardrum —There is no good topical anesthetic for the eardrum because the external layer of the eardrum is squamous epithelium derived from skin Unlike mucous membranes which can be anesthetized with topical anesthetics the unbroken skin and its derivatives are resistant to them Hence no solution of cocaine, tetracaine (Pontocaine), dibucaine (Nupercaine), or any other topical anesthetic is effective on the eardrum However, if there is a perforation of the eardrum or if its surface epithelium is abraded or infected the common topical anesthetics induce their effects

Bonain's solution is an old preparation which induces good anesthesia of the eardrum It consists of equal parts of phenol, methol and cocaine alkaloid The constituents are crystals, but when mixed they form a thick brownish liquid When the solution is applied to the drumhead with a small piece of cotton and left in place 5 or 10 minutes, satisfactory anesthesia develops, but care must be taken because ischemia with permanent damage to the eardrum can also ensue

Topical Anesthesia of the Nose and Paranasal Sinuses —In the nose topical anesthesia is often produced by use of "cocaine mud," made by mixing 0 3 Gm of cocaine flakes with aqueous Adrenalin solution (1 1,000) The thick syrup produced is taken up on cotton tipped wire applicators which are inserted into the nose Usually one applicator is placed near the sphenopalatine ganglion and the other near the anterior ethmoidal nerve As in all situations requiring local anesthesia, it is very important to wait long enough for the drug to act

Topical Anesthesia of the Larynx —For topical anesthesia of the larynx cocaine or tetracaine (Pontocaine) is ordinarily used For lighter anesthesia lidocaine (Xylocaine) is satisfactory Two methods may be used The first is to apply 5 or 10 per cent cocaine solution or 1 or 2 per cent Pontocaine solution on

Status Asthmaticus.—Corticosteroids may be the only drugs which are effective; their intravenous administration can be lifesaving.

Angioneurotic Edema.—Edema due to allergic reactions may threaten the patient's life if laryngeal tissues swell sufficiently. Intravenous injections of corticosteroids or their local infiltration may be lifesaving.

Bell's Palsy.—There have been favorable reports regarding the corticosteroids in Bell's palsy. By reducing inflammatory reaction corticosteroids are said to restore function sooner than would otherwise occur.

Caustic Burns of Esophagus.—By utilizing that action of corticosteroids which delays fibroblastic proliferation, caustic burns of the esophagus are permitted to epithelize before scar tissue contracture develops. Esophageal dilatation is also required.

Erythema Multiforme.—Erythema multiforme, really a dermatologic condition, is frequently detected first by the otolaryngologist because of oral manifestations. Treatment with corticosteroids usually produces amazingly rapid relief but remissions often occur after treatment is discontinued.

Midline Lethal Granuloma.—This unusual and commonly fatal disease usually responds well initially to corticosteroids. The destruction of the midline facial structures stops and tissues heal. Sometime thereafter the disease usually progresses and then often fails to respond to even higher doses than were successful at first.

ANALGESICS

There is little which is new or different about analgesics in otolaryngology that does not apply to other specialties. Aspirin affords relief for most pains. For more severe pain, e.g., in acute external otitis or acute tonsillitis, 30 mg. of codeine may be needed. Rarely is an injection of morphine or meperidine (Demerol) required. It should be noted that 50 mg. of Demerol given by mouth is generally less effective than 30 mg. of codeine. Combinations of tranquilizers and mild analgesics have worked well in some patients.

Local analgesia for the throat and oral cavity is obtained by lidocaine (Xylocaine viscous) or by dyclonine (Dyclone). Formerly patients with severe laryngeal pain, e.g., those with tuberculous laryngitis, were given sips of cocaine solution before mealtime but the less toxic local anesthetics are now used.

ANESTHETICS

General Anesthetics

General anesthesia for otolaryngologic patients presents problems not encountered in anesthesia in other fields. The airway must be maintained with special care because often there is blood in the pharynx during the operation. The endotracheal tube is therefore important. Deep anesthesia is generally not required since complete muscular relaxation is not essential.

Topical Anesthetics

Topical anesthetics are of greater importance in otolaryngology than in most specialities. Correct use of any potent topical anesthetic means that only as much

is cleared by antibiotics In recurrent cases, adenoidectomy is necessary for permanent relief

DRUGS FOR TINNITUS

Ringing in the ear is a very common complaint which is very difficult to treat When the condition is caused by impacted cerumen in the external ear or serous otitis media (both infrequent causes), the tinnitus stops when the plug is removed or the eustachian tube is opened In most instances, however, tinnitus is due to disease of the inner ear or of the central connections, and treatment is difficult, if not completely ineffective Vasodilators such as nicotinic acid and intravenous histamine may be tried but these measures seldom, if ever, relieve the head noise The patient needs strong reassurance that he is not becoming deaf or that he has not had a stroke, although both of these conditions may, indeed, be associated with tinnitus

MÉNIÈRE'S DISEASE (ENDOLYMPHATIC HYDROPS)

This important otologic disease is discussed in Chapter 19

POSTOPERATIVE MEDICATION

The only special point about postoperative medication in otolaryngologic patients is that the cough reflex must not be too deeply depressed It is better for the patient to have some discomfort than to be narcotized so deeply that he is endangered because he cannot cough at all Codeine, 30 mg, which depresses cough also usually controls pain on the first postoperative day On the day of operation however most otolaryngologic patients may need morphine or Demerol for their pain as well as cough

VASOCONSTRICTORS AND DECONGESTANTS

Vasoconstrictors are used in otolaryngology to stop bleeding and to open the nasal airway

Epinephrine (Adrenalin) —This very potent agent is widely and well used for nosebleed and in bleeding from the postoperative tonsillar or adenoid fossa Such bleeding usually responds well to packing with a tampon soaked in aqueous Adrenalin solution, 1 1 000 Larger vessels should of course, be ligated

Ephedrine —Ephedrine (3 per cent), applied to cotton tampons or used as a nasal spray, is a good vasoconstrictor for office use As a nosedrop, the ½ per cent concentration is generally preferred Ephedrine may produce undesirable central stimulation The drug is not effective for more than 30 to 60 minutes

Phenylephrine (Neo-Synephrine) —In ¼ and ½ per cent strength this is the most commonly used nosedrop The action on nasal cilia is not deleterious and the drops are well tolerated but the duration of the action is brief

Naphazoline (Privine) —Although Privine is one of the longest acting and effective vasoconstrictors, it unfortunately is followed by strong rebound reactions so that many patients who used these nosedrops for a week or longer may become

an applicator for about 3 minutes in each pyriform recess The second method is to spray the larynx 2 or 3 times, at intervals of 2 or 3 minutes, with the cocaine or Pontocaine solution The direct application is more certain

The trachea is anesthetized by instillation of one of the topical anesthetics When the patient coughs, the solution is distributed over the mucosa This technique often gives adequate anesthesia for bronchoscopy, but sometimes, once the bronchoscope reaches the carina, additional anesthesia is needed Here a spray bottle with a very long cannula or a cotton tipped bronchial applicator may be used

DRUGS FOR NOSEBLEED

In nosebleed, conditions that are rarely the cause of nosebleeds require as much emphasis as those that are common causes Physicians who are not adept at intranasal packing and cautery often attribute nosebleeds to a disturbance in the blood clotting mechanism Depression of vitamin K, vitamin C blood levels, prothrombin content of blood, bleeding time, or clotting time are not, however, commonly associated with epistaxis When epistaxis is due to systemic causes such as scurvy, leukemia, or a change in the blood prothrombin content, the patient bleeds from other mucous membranes into the skin and the viscera as well Drug hemostasis in nosebleeds is often dangerous because it may lead the physician to rely upon medical treatment for a surgical condition

Epinephrine (Adrenalin)—Adrenalin, aqueous 1 1,000, is of great value in treatment of the usual nosebleed from the anterior part of the nasal septum Applied on cotton and pressed hard against the bleeding point, it produces local vasoconstriction in a few minutes and the bleeding usually stops The nose can then be examined and the bleeding vessel cauterized There are no significant systemic reactions from Adrenalin applied topically in the nose the drug is safe to use even in older patients

Morphine—In doses adequate to produce relaxation and mild euphoria, morphine is a valuable drug for patients with severe nosebleed It is not to be used when bleeding can be readily controlled with simple cautery, but only for the patient who needs a postnasal pack or hospitalization

Chemical Cautery—Silver nitrate fused on the end of wooden applicators is an excellent agent for cautery of a bleeding vessel It may be used without topical anesthesia in many patients Another effective chemical cauterant is trichloracetic acid

DRUGS FOR DEAFNESS

Except occasionally in Meniere s disease, nerve deafness is not helped by drugs Many instances of conductive deafness are surgical matters and do not require, or respond to, medical treatment However, otitis media is a common cause of conductive deafness which does not respond to antibiotics When cerumen has occluded the ear canal, instillation of hydrogen peroxide or any oily drops will soften it so that it can be washed out more easily Hearing should improve

Serous Otitis Media—In serous otitis media due to obstruction of the eustachian tube by infected adenoid tissue, hearing is restored when adenoiditis

THE CHOICE OF DERMATOLOGIC DRUGS

Marion B Sulzberger, M D

INTRODUCTION

The problems and procedures of the dermatologist are often unique and may appear to be quite heterodox to those who have no knowledge of the specialty Prescriptions directions, rules, methods and equipment designed for and admirably suited to other branches of medicine often do not fit the specialty of dermatology Conversely some of the most useful dermatologic therapeutic measures are of little interest and less use in other fields The following are among the reasons which account for the unusual position of dermatologic therapy

1 The skin is unique in that its reactions in health and disease are the measurable resultants not only of the action of substances and influences coming from within but are, to the very highest degree, the products of all the ever changing forceful impacts coming from the outer world

2 The skin is unique in that it presents a microcosmos of almost all the problems of medicine and of surgery Almost every known diagnostic and therapeutic approach every pharmaceutical agent, and every physical or surgical procedure has not only its place but often its special modification in the management of the skin and its diseases

3 In addition, the skin is unique in that the management of its diseases demands special procedures which are almost, if not entirely, the sole province of dermatology Among these are the special diagnostic techniques for demonstrating fungi burrows and mites and for testing the skin's reaction to allergens, light, heat, cold, stroking and other stimuli, or the special therapeutic procedures for superficial radiation, for the excision or the freezing, fulguration, desiccation, or cauterization of benign or cancerous skin tumors and other lesions, for flattening scars for bleaching or darkening pigment, for removal of hairs, and, to close a list which could be expanded almost ad infinitum the special procedures and the special pharmacology for the repeated topical, localized, and direct application of medicaments to the skin lesions themselves

It is this last listed highly specialized form of dermatologic procedure which will constitute a good part of the present chapter Just as the causal factors of

virtually addicted The nose closes completely from the rhinitis medicamentosa, and only Privine can reopen the passages

Propylhexedrine (Benzedrex) Inhaler.—This popular device does a good job of vasoconstriction and decongestion If the patient does not receive too much psychic stimulation, there appears to be no contraindication to its use

Cocaine.—A 2 per cent solution of cocaine is an excellent nasal vasoconstrictor for office use The mild anesthesia produced is often useful when minor intranasal manipulations are necessary

Comment.—In general, nosedrops are useful for symptomatic relief of acute nasal obstruction, but they should not be used for prolonged periods In patients with chronic nasal obstruction, there almost always is better medical or surgical relief available Nosedrops probably do little to improve drainage in acute sinusitis Oily nosedrops, once very popular, have fallen into disrepute because of the rare case of lipoid pneumonia

SELECTED REFERENCES

Cullen, S C, and Santos, C C Analgesia for Postoperative Pain Without Respiratory Depression, Anesthesiology 16 674, 1955

Flynn, Thomas F The Uses and Abuses of the Adrenocortical Steroids in Otolaryngology, A M A Arch Otolaryng 64 203, 1957

Heinberg, C J [illegible] in Otolaryngologic Practice, A [illegible]

Saunders, W H [illegible]

Saunders, W H [illegible] iagnosis, Ann Int Med. 47 [illegible]

Saunders, W H, Suie, Ted, and Sroufe, S A The Microflora and the Treatment of External Otitis and Otitis Media, Postgrad Med 25 176, 1959

rather unorthodox, fashions in particular dermatoses (e g, sulfapyridine and sulfones in dermatitis herpetiformis, antimalarials in chronic discoid lupus erythematosus, hormones and antibiotics in acne vulgaris, and steroids in eczematous eruptions)

2 Certain agents are classed merely as bleaches, antipruritics, antipsoriatics, antieczematous agents, or keratolytic agents These classifications are not "unscientific" or vague but indicate that dermatologic local therapy has scientifically demonstrated such agents to be the most effective in the mentioned dermatologic state or disease, just as internal medicine has demonstrated acetylsalicylic acid to be effective against certain fevers or headaches, or digitalis preparations against certain anomalies of cardiac function However, since many drugs have a variety of dermatologic effects and several different indications in dermatology, they will perforce be listed repeatedly and under the heading of each of their particular fields of usefulness This necessitates considerable duplication and repetition, but such duplication is considered necessary for the sake of simplicity and clarity, being distinctly preferable to the many cross references which would be required were each drug mentioned in one place only For in that case the physician attempting to find the drugs of choice for treating a given dermatosis would constantly be turning the pages in order to find them and would nowhere find them conveniently assembled in one section

3 The many prescription mixtures given in detail are essential in dermatologic topical therapy and are logically and scientifically compounded of selected ingredients, each having its special purpose and function To write simply, "Use 6 per cent ammoniated mercury as a bleach" or "1 per cent chrysarobin as an antipsoriatic" would make things much easier for the author but would serve no useful purpose for the practitioner unless accompanied by the precise formulation of the vehicles, adjuvants, etc, with which the drug of choice must be prescribed In short, in dermatology it is the *complete prescriptions which are matters of choice*, not merely the active drugs themselves

In many instances there are available complete modern dermatologic prescriptions which are supplied as "ethical products" by reliable manufacturers of pharmaceuticals Often these "proprietaries" have greater stability, uniformity, and "elegance" and may even cost less to the patient than the equivalent dispensed on prescription by a local pharmacy In such instances, I have not hesitated to give the trade names of the proprietary mixtures

According to the best figures available today, about 1 patient in every 7 comes to the general physician because of a complaint in the field of dermatology Fortunately, however, about 90 per cent of these legions of sufferers are affected by some dermatosis falling within one of the 10 or 12 commonest categories of skin diseases It is within these most common categories of skin diseases that the practitioner will find his field of particular usefulness, and it is for the general run of cases in these common categories that the drugs of choice in this chapter have been assembled and discussed In the present arbitrary selection of cutaneous entities and measures for their treatment, more diagnoses have been omitted than mentioned, and more dermatologic remedies are left out than included However,

dermatoses are commonly of both internal and external origin, so also skin diseases must generally be treated both from within and from without Soporifics, sedatives, and tranquilizers, "antibiotics" and other anti-infective agents, anesthetics, antiallergic and anti-inflammatory agents, vitamins and diets, hormonal preparations, and all the measures and medicaments of medicine in general must be constantly and properly used in dermatologic therapy Sometimes the usual medical and systemic measures are used in the usual fashions, not infrequently they must be modified and adjusted to fit the peculiarities of the specific problems of the skin disease Despite the ever-growing importance of the systemic medical approaches, the fortunate circumstance that potent and effective medicaments can be applied directly and repeatedly to the skin lesion itself still remains one of the mainstays of dermatology This advantage, coupled with the fact that objective critical and comparative observations with the unaided naked senses can be used to evaluate the effects of each such application, has led to the development of unusually effective and scientifically controllable forms of therapy For example, dermatology is unique in that two or more similarly affected symmetrically situated skin sites can be treated simultaneously with different topical medicaments, and the results compared by both clinical and laboratory procedures, hourly, daily, weekly, or at any other chosen intervals This is known as the method of "simultaneous symmetrical paired comparison"

In view of these advantages, it is not astounding that through many decades of careful use and controlled evaluation of the effects of topical medication, dermatologists have often discovered and adopted fundamental rules of therapy some time before they were apparent to practitioners in other branches of therapeutics

Thus preparations containing combinations and mixtures of medicaments with similar or additive effects have long been used and are still among the standard and most efficient of topical agents For dermatologists long recognized that they could combine, for example, phenol and menthol (as antipruritics), or resorcin and sulfur, or mercurials and salicylic acid (as keratolytics), etc, and thus achieve a summation and sometimes even a potentiation of therapeutic effectiveness without an accompanying augmentation of undesirable irritations, toxic effects, or allergic sensitizations Then, again, since external therapy makes the most exigent demands upon the physical and other properties of the topical preparations and vehicles, these properties—their staining, sting, or stench, their viscosity, thickness, stickiness, melting point, stability of emulsion, etc—are matters of major consequence In order to achieve the optimum in all these respects it is often necessary to select carefully and to compound and mix together in a single prescription a variety of different powders, greases, oils, emulsifiers, wetting agents, coloring agents, etc

This rather long preamble is intended mainly to make the following matters clearer to those who consult this chapter

1 While practically all drugs have their indications in dermatologic therapy, the present chapter will be devoted almost entirely to those for topical application Since systemic medicaments are fully covered in other chapters of this text, these will be discussed here only when they are to be used in specialized, sometimes

rather unorthodox, fashions in particular dermatoses (e g, sulfapyridine and sul fones in dermatitis herpetiformis, antimalarials in chronic discoid lupus erythematosus, hormones and antibiotics in acne vulgaris, and steroids in eczematous eruptions)

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it is hoped that in this chapter will be found most of the simple medicaments which can be tried first in most of the common and more readily diagnosable dermatoses *

ANTIACNE AGENTS (Agents Used in Acne Vulgaris, Acne Rosacea, and Other Acneiform Eruptions)

Resorcinol and Sulfur —Resorcinol—as a reducing agent—keratolytic and antiseptic is used in 2 to 6 per cent in shake lotions, creams, and pastes Sulfur precipitate—as a reducing agent—keratolytic and antiseptic is used in 3 to 10 per cent in shake lotions creams, and pastes Resorcinol and sulfur precipitate are usually combined in order to summate their therapeutic effects without summation of irritancy

REPRESENTATIVE PRESCRIPTIONS —

	Gm or ml unless otherwise indicated†
℞	
Resorcinol	2 0 to 6 0
Sulfur precipitate	3 0 to 6 0
Zinc oxide	
Talc aa	*20 0 to 25 0*
Glycerin	10 0
Water	
Alcohol aa	40 0
S Antiacne shake lotion apply at night and wash off in morning	

[May be made skin-colored (cuti color) and used by women duri g the day by the addition of bentonite and oxides of iron (Almay Neutra color) 2 0 to 4 0, and the substitution of pre pared calamine for the z nc ox de]

℞	
Resorcinol	0 6 to 1 8
Sulfur precipitate	0 9 to 3 0
Rose water ointment ad	30 0
S Antiacne cream apply at night and wash off in morning	

℞	
Resorcinol	0 6 to 1 8
Sulfur precipitate	0 9 to 3 0
Paste of zinc oxide ad	30 0
S Antiacne paste apply at night wash off in morning	

The concentrations of resorcinol and precipitated sulfur must be adjusted and readjusted to bring about slight but not uncomfortable or unsightly dryness and scaliness of the skin In the shake lotion of the first prescription the quantities and rat os of the other ingredients must be varied to achieve the desired shade thick ness etc

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Med [illegible]

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		Gm unless (indic
℞		
	Resorcinol	2 0
	Sulfur precipitate	3 0
	Zinc oxide	
	Talc āā	20 0
	Glycerin	1(
	Water	
	Alcohol āā	4(
S	Antiacne shake lotion apply at night and wash off in morning	

[May be made skin-colored (cuti-color;

℞		
	Resorcinol	0 6
	Sulfur precipitate	0 9
	Rose water ointment ad	3(
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℞		
	Resorcinol	0 6
	Sulfur precipitate	0 9
	Paste of zinc oxide ad	3
S	Antiacne paste apply at night wash off in morning	

℞

Sulfurated lime solution (Vleminckx' solution)
Lime 16 5
Sublimed sulfur 25 0
Water sufficient to
boil down to 100 0
Must be freshly prepared

S 1 tablespoonful (16 ml) to 1 pint of hot water to make approximately 1 32 dilution applied as hot wet compresses ½ hour several times daily in cystic and pustular acne
[Action and Uses Keratolytic, anti inflammatory, antibacterial]

It is often advantageous to prescribe Vlem-Dome Powder Packets to assure a fresh and active preparation

℞

Vlem Dome Powder Packets

S 1 powder to each quart (weak), or pint (strong), of hot water (as hot as the skin will tolerate) Apply with cloths as wet compresses for 15 to 30 minutes 2 to 4 times daily Use a glass or porcelain, not a metal container Remove all jewelry, silver, etc, from person and room where solution is prepared and used, and avoid getting solution into eyes

Quinolor —

℞

Compound Quinolor Ointment
Oxyquinolin sulfate
Oil of white thyme
Eucalyptol āā 0 5
Petrolatum ad 100 0
[The benzoyl peroxide has been omitted because of danger of explosion while compounding]

This ointment is very useful as a nightly application in many cases of acne vulgaris it is best started in dilute form by prescribing 1 part of Compound Quinolor Ointment to 2 parts of petrolatum, then, if tolerated, equal parts of the quinolor ointment and petrolatum, and finally the undiluted Compound Quinolor Ointment

Estrogenic Therapy.—In otherwise entirely healthy young women (carefully examined especially as to their mammary and genital state before and regularly during period of administration) mild estrogenic therapy may be useful It may generally be instituted with safety after the age of 16 or 17 to prevent exacerbations of acne vulgaris

If tolerated, effective, and without contraindications, this treatment can be continued during the entire "acne age" (usually into the early twenties)

Antibiotics —Oral administration of antibiotics, e g , tetracycline oleandomycin, etc , in doses of 250 mg , at the beginning 4 times daily and gradually reducing to once daily or less, is often effective and well tolerated Antibiotic treatment should be accompanied by regular examinations of the patient, including periodic complete blood counts, routine urinalyses etc Provided no adverse effects appear, the administration of antibiotics can be continued if necessary during the entire "acne age" and in the minimum dosage required to suppress the acne eruptions ("morbidistatic" doses)

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[May be made skin-colored (cuti color), and used by women during the day, by the addition of bentonite and oxides of iron (Almay Neutra color) 2 0 to 4 0, and the substitution of prepared calamine for the zinc oxide]

℞	
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Rose water ointment ad	30 0
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*In closing this introduction I wish to express my gratitude to Drs Frances Pascher, Rudolf L Baer, Alfred Pelzig and H H Sawicky and to Miss Claire E Isenstein and to Mr Paul Hoeber for the help I received from the invaluable data in the second edition of Dermatologic Formulary of the New York Skin and Cancer Unit (Paul B Hoeber, Inc., Medical Book Department of Harper and Brothers, New York, 1937)

†Throughout this section the numerals in the prescriptions ... unless specified otherwise

℞

Ammoniated mercury	1 8
Zinc oxide	
Bismuth subnitrate aa	6 0
Lanolin	
Petrolatum āā ad	30 0

S Apply to hyperpigmented skin areas by gentle massage before retiring and leave on overnight

℞

Benoquin ointment

	7 5
	30 0

S ... reas by ... ave on overnight

[If tolerated, the half strength and finally the full strength Benoquin ointment may then be prescribed]

Both of these bleaches are strong sensitizers and thus the potential causes of allergic contact type dermatitis The mercurials are also capable of producing systemic poisoning and should not be applied to large areas or for long periods of time without regular medical supervision

Of course, the protection of hyperpigmented skin areas from exposure to sun light will in many cases cause some diminution of the amount of pigment and dis figurement Change of habits, the use of covering clothing, of sun screening prepa rations, and of all the other measures for reducing the skin's exposure to light are therefore of some slight value in managing certain patients suffering from hyper pigmentations (See section on 'Sun Screens," page 771)

AGENTS USED IN BULLOUS DERMATOSES

The most important representatives of the bullous dermatoses are pemphigus, dermatitis herpetiformis, and erythema multiforme bullosum While these may present large bullae, there are numerous variants and stages in which frank clinical bullae are absent Clinical diagnosis is therefore often a specialized task, and in many cases special adjuvant laboratory and other methods may be required

Pemphigus —Modern therapeutic advances have transformed pemphigus from a practically invariably fatal disease into one in which early adequate manage ment can prolong the lives in most cases and perhaps ultimately save the lives in many Modern treatment consists essentially in the administration of cortico steroids and/or ACTH, in *whatever* doses necessary to bring about control of the eruption, together with all modern measures to prevent, reduce, or counteract the undesirable effects of prolonged high dosage of these hormones (low salt diets, anti biotics, antacids, antidiabetic measures, tranquilizers, psychiatric approaches, surgi cal interventions, potassium supplements, anabolic agents, and others)

Opinion is still divided as to whether it is advantageous to combine or alternate ACTH injections with the oral corticosteroid therapy In my consider able clinical material of ambulatory patients, I have found that corticosteroid therapy alone was usually as effective and safe as the combination with ACTH

Miscellaneous Measures —In addition to, and sometimes as important as, any of the foregoing are the regular scrubbings with soap and hot water, the dietary prohibitions, the selection of proper clothing, and the elimination of external acnegenic irritants and internal acnegenic drugs (e g, iodides, bromides) More important still, no otherwise refractory case which is severe or tends to scarring should ever be deprived of the benefits of x-radiation, which, when all else fails, is often effective and is absolutely safe when given by experts such as qualified dermatologists (Of course, the gonads must be properly shielded)

Scarring —One of the relatively common and most serious sequelae of acne is the scarring, which can occur principally on the face, back, and chest This often produces permanent physical and psychic handicaps The best modern technique for improving the appearance of patients with severe acne scarring of the face is the dermatosurgical method of "plastic planing" or "dermabrasion" as employed by dermatologists in carefully selected cases This, like all other minor surgical and physical procedures in acne and other dermatoses falls outside the scope of a book on drugs

Chemosurgery —In certain cases, however, a degree of improvement of facial acne scarring can be obtained by the use of peeling drugs according to the older dermatologic techniques ('Chemosurgery' is an appropriate term introduced by F Mohs, which is applicable to all such chemical means for removing tissue) Examples of chemosurgery for acne scarring include the application of liquid phenol or trichloracetic acid or of resorcinol containing pastes or of solid carbon dioxide ("dry ice") in various forms (including its mixture with acetone sufficient to make a "sherbetlike" consistency)

All of these peeling measures are quite safe when the necessary caution is used and specific precautions are observed They can be fairly effective when applied and reapplied by experienced specialists in proper fashion at correct intervals and in carefully selected appropriate cases only It is doubtful, however, whether the nondermatologist will generally wish to devote the time and study necessary to ensure the safety and usefulness of these or any other chemosurgical 'keratolytic methods

BLEACHES

The bleaching of *hair* is best accomplished by the usual cosmetic procedures using peroxides, especially solution of peroxide of hydrogen followed by alkalinizing agents such as ammonia water Many effective commercial preparations are available and quite safe when properly applied The bleaching of *hyperpigmented skin areas* is quite another matter, and there are as yet no really effective and completely safe drugs for this purpose

Unless the hyperpigmentation is directly attributable to endocrinologic, dietary or other sources (e g, ovarian, adrenal, or pituitary disease, hyperpigmentation of pregnancy, of pellagra, etc) no causal, internal or surgical therapy is possible and the external application of topical bleaching agents is the sole approach

The preparations of choice are of two kinds—mercurials or hydroquinones—especially, ammoniated mercury or the monobenzoylester of hydroquinone Representative prescriptions follow

Dermatitis Herpetiformis.—Unfortunately this polymorphous and usually extremely itching and burning dermatosis can present itself in many guises and forms which are, even for the expert, difficult to diagnose clinically. According to the form, stage, signs and symptoms the treatment includes the topical and systemic antipruritic and anti-inflammatory measures outlined in the sections on Antieczematous Agents and on Antipruritics. However, the most important aspect of the therapy of dermatitis herpetiformis is the proper use and choice of the morbidistatic systemic medicaments. The drug of choice is

℞
Sulfapyridine tablets 0.5
S. In divided doses after meals 4 to 8 or more tablets daily as required to achieve and maintain control of the eruption. Reduce dose to minimum required to maintain morbidistasis.

All the necessary measures to prevent or reduce the possible ill effects of this medication should be carried out (e.g., 1.0 Gm. of bicarbonate of soda with each gram of sulfapyridine, regular examinations of the blood and urine, and others).

Other sulfonamides, alone or in combination, can be tried when sulfapyridine cannot be tolerated. While they may be better tolerated, they are usually inferior to sulfapyridine in effectiveness in dermatitis herpetiformis. The sulfones as well as corticosteroids have a place in some cases which do not respond to or cannot tolerate sulfapyridine.

℞
Sulfoxone sodium tablets 0.33
S. 1 tablet 2 to 3 times daily. Reduce to lowest morbidostatic dose. [Blood studies before and regularly during treatment.]

℞
Promacetin tablets 0.5
S. Daily dose of 3.0 to 4.0 Gm. in divided doses. Reduce to maintenance dose or less as soon as possible. Precautions as with preceding prescription.

℞
Hydrocortisone tablets 20 mg.
S. 4 to 10 tablets daily as required.

As of today it appears that in this disease, as in so many other dermatoses, triamcinolone may be the most effective of the available steroids. It is given in the ratio of about 3 to 4 mg. of triamcinolone as equivalent to 20 mg. of hydrocortisone.

The oldest classic remedy is arsenic in various forms. This is now little used because of the risks of early toxicity and late sequelae. A usual form of prescription follows:

℞
Potassium arsenite solution
(Fowler's solution) 10.0
Peppermint water q.s. ad 30.0
S. 1 drop after each meal in ½ glass of water. Increase the after-meal dose by 1 drop each day until 30 to 40 drops are being taken 3 times daily. Then reduce the after-meal dose by 1 drop daily.

This course of arsenical can be repeated several times if necessary.

Heroic measures and heroic doses are completely justified in cases of pemphigus, as it is obviously better to have the patient alive with a gastroduodenal ulcer, a transitory psychosis, diabetes, or a pathologic bone fracture (all of which can today be treated with hope of success), than to have the patient die of pemphigus In general, the initial dose of oral steroid must be a very large one in order to gain control of the severe case This large initial dose can usually be reduced gradually and a maintenance dose of much smaller size reached and continued In most patients finally under satisfactory control on lower doses, there will occur sporadic short periods when the relatively low maintenance dose must be temporarily but materially increased in order to combat situations of stress or "escapes" and "break-throughs" of the disease due to various ascertainable or unascertainable causes In some cases the final maintenance dose is very small, and in some the pemphigus seems to burn itself out" and the patient requires no continuation of therapy In other words *the dread and classic example of fatal disease, pemphigus, is not generally fatal, provided the patient can be kept alive long enough to allow nature's curative forces to master the disease* Representative drugs and dosage schedules follow

℞

S

break through of the dermatosis appears, and then raise the dose to the minimum which

According to specific indications instead of hydrocortisone, oral cortisone acetate or oral prednisone, prednisolone, triamcinolone, Medrol, or dexamethasone may be substituted in the biologically equivalent doses That is, 25 mg of cortisone acetate or 5 mg of prednisone or prednisolone or 4 mg of triamcinolone or Medrol can be given in the place of each 20 mg of hydrocortisone The delta steroids will be *especially indicated* in cases *where salt and water retention* are the imminent dangers and be *especially contraindicated* where *gastrointestinal hyperfunction and ulceration* are the paramount hazards

In place of oral corticosteroids (or alternating with them), ACTH may be used as follows

℞
Repository corticotropin injection
S 20 to 100 mg once to twice daily (gradually reducing dosage as described above for hydrocortisone)

When the dermatosis proves refractory to the procedures mentioned or when the situation is extremely grave or death seems imminent, the administration of necessary doses of corticotropin solution (ACTH) should be given in 500 ml glucose solution by slow intravenous drip

Intravenous Medrol (Solu Medrol) and depot Medrol intramuscularly are newly introduced forms of corticosteroid administration which show promise

This preparation is highly irritating and like all the other caustics listed should never be applied except by physicians well acquainted with the technique, the risks and the essential precautions

ANTIECZEMATOUS AGENTS

These include the following agents used in eczematous and eczematoid dermatoses e g allergic eczematous contact dermatitis, simple inflammatory dermatitis from chemical or physical causes atopic eczema or atopic dermatitis in infants ('infantile eczema'), children adolescents, or adults, nummular eczema, circumscribed lichenified dermatoses (such as circumscribed lichen simplex, circumscribed neurodermatitis) and eczematized eruptions in general

Since most eczematous and eczematoid eruptions itch, and many itch very severely the antipruritic measures given on page 757 are indicated in this group also Moreover in the large number of cases in this category which are due to chemical or physical agents and allergens the discovery and reduction or elimination of exposure to the causal agents are obviously the most fundamental therapy Dermatologic radiation (grenz ray, superficial x ray, thorium X) is also often one of the very best modes of treatment For reasons such as these, the etiological diagnosis and proper therapy of the persistent cases of 'eczema often become matters requiring specialistic skills and equipment However, local external treatment coupled with systemic sedation tranquilization antihistaminic administrations and as a final resort systemic corticosteroid therapy are still among the most potent weapons These measures are often adequate, especially in self limited eczematous conditions (e g plant dermatitis and atopic dermatitis in infants children and adolescents)

Selection of correct local external treatment depends not so much upon the cause as upon the site, the extent and the stage of the eruption (e g acute and angry or subacute or torpid, thickened and lichenified) Finally, the drug of choice depends upon which agents the physician finds by systematic trial to be most effective and best tolerated by the individual and site

Acute and Angry, Bright Red, Swollen Blistering Oozing or Weeping Eruptions —Wet applications should be applied as open wet compresses immersions or soaks To be most effective these require great skill and patience and *special nursing techniques* The dressings must never be allowed to become warm or to dry out Usually the applications are made in periods of ½ to 1 hour and repeated 4 to 6 or more times daily

Approximately Physiologic Saline Solution

℞
Sodium chloride 0 5%
In distilled water 100
S Keep in basin at room temperature and apply by means of sopping wet smooth cloths Keep changing continuously never *allowing cloths to* dry out or become worn

℞
Fresh milk
S As for above prescription
(An excellent O/W emulsion almost always available in an emergency)

Erythema Multiforme Bullosum.—In the bullous form of erythema multiforme, the treatment is similar to that outlined for pemphigus In milder cases, local treatment, antihistaminics, calcium preparations, sedatives, and antipruritics will usually suffice

The search for possible causes is here essential, as many cases are due to drugs, e g, salicylates, iodides, bromides, barbiturates, antibiotics, and innumerable other common and unusual medicaments, or to other allergens, or to foci of infection, such as streptococcal, tuberculous, or viral infections of systems or organs other than the skin

The local treatment is analogous to that specified under eczematous dermatitis (page 736)

Calcium is best administered in the following forms

℞
Calcium gluconate solution 10% 10 0
S For intravenous use Inject contents of one ampule slowly 1 to 2 times daily

℞
Calcium gluconate tablets 1 0
S 1 tablet 3 times daily before meals

Salicylates in the usual forms are also sometimes useful

CAUTERIZING AGENTS (Caustics)

These are used to destroy warts, condylomata, keratoses, xanthelasma and certain forms of moles when carefully selected and diagnosed as safe by experienced specialists They can also be used to produce peeling (a specialistic procedure)

℞
Monochloracetic acid solution
(to prepare—add a few drops of distilled water to 1 Gm of monochloracetic acid crystals)

℞
Trichloroacetic acid solution
(to prepare—as above)
S Apply with sharply pointed applicator stick surrounded by wisp of cotton Application must be strictly confined to area or lesion to be destroyed

℞
Liquefied phenol (i e , 95%)
S Apply with applicator stick and cotton to area to be peeled or removed Beware of phenol poisoning by absorption and by inhalation! [Selected cases! small areas! good ventilation!]

Podophyllin or, better, podophyllum resin can be used to cauterize and destroy the lesions of hypertrophic lichen planus and torpid cornified circumscribed neurodermatitis (lichen simplex circumscriptus) but is most valuable in treating condylomata acuminata of the genitoanal areas

℞
Podophyllum resin 10%
in compound tincture of benzoin
S Apply to lesions but keep away from normal skin!

Resorcinol 2% to 3%
(as "reducing," drying, antiseptic and desquamating agent)

in

Zinc oxide 15%
Talcum āa
Glycerin 10%
Dilute alcohol (50%)
q s
[Medicaments listed above can be added to this base as indicated for the specified effects, either alone or in combination]
S Medicated shake lotion Shake bottle well and paint on affected areas two, three, or more times daily with a large flat paint or varnish brush

℞
(Combinations of menthol, phenol, solution of coal tar, resorcin, and benzocain can be added as specified in above prescription)
Zinc oxide
Talcum
Lanolin (anhydrous) āa 15%
Olive oil (or sesame, cotton seed, etc., oils) 50%
Tween 80 (polysorbate) 3%
Solution of aluminum acetate 3%
Water q s
S Medicated emulsion—paint on 2, 3, or more times daily with flat, wide paint or varnish brush

℞
(Combinations of menthol, phenol, solution of coal tar, resorcin, and benzocain can be added as specified in above prescription)
Triethanolamine 3%
Lubriderm (unscented) q s
S As for above prescription

Subacute to Chronic, Torpid, Thickened Lichenified Eczemas and Eczemato Conditions—When the eruptions are widespread, the baths, shake lotions, a emulsions specified above are often the most practical means of getting effect therapy repeatedly and efficiently to all areas

Tars, and especially coal tar preparations, have long been sovereign remed in chronic eczemas and lichenified dermatoses The "unrefined" crude coal tar generally more effective than the decolorized and "refined" products Among drawbacks are its odor and staining properties and its tendencies to produce follic litis on hairy areas and photosensitization dermatitis in some cases The folliculi can sometimes be avoided by combining the coal tar with antiseptics such as ar moniated mercury or quinolines or antibiotics

℞
Crude coal tar 2% to 10%
{ Ammoniated mercury 3%
or
Vioform 3% }
Zinc oxide ointment ad 30 0
One of the medicaments in brackets can be included to reduce tendency to pyodermas
S Apply to affected areas 2 or more times daily

℞
Solution of aluminum acetate 5% to 10% in water (Burow's solution modified) (Freshly prepared)
S As for above prescription

Convenient proprietary forms are

℞
Domeboro Powder
or
Domeboro Tabs
or
Buro-Sol Powder
One tablet or one package of powder to a pint or quart of water is the usual range of proper concentrations

Where the lesions are inclined to be purulent and infected ('impetiginized') or where greater drying is required (as in fungous infections and intertrigo), the following are indicated

℞
Potassium permanganate tablets 0 3
S 1 tablet to 2 quarts (or 2 liters) of water (Approx 1 6 000 solution for wet compresses or foot and hand soaks)
or
For baths (estimated 50 gallons or 400 liters to tubful of water)
S 20 to 30 tablets to the tubful of water (Roughly 1 60 000 to 1 40 000 solution)
[N B Be sure to dissolve thoroughly before adding to bath preferably in a milk bottle or other container Contact of the skin with undissolved particles can cause severe burns!]

℞
Cornstarch (hydrolyzed)
e g Linit starch (unscented) (1 pound to tubful of water)
S Starch bath for soothing and softening

℞
Oatmeal bath
Aveeno
S Oatmeal bath for soothing and softening
1 package to tubful of water

(See warnings regarding slipperiness of tub on page 746)

[Medicated baths e g with tars as listed under section on Antipsoriatics on page 760 may prove useful also in generalized eczematous processes]

In generalized or widespread cases, where wet compressing is not feasible and in subacute to chronic eczematous dermatoses the following shake lotions and *emulsions find their indications*

℞
Menthol ¼% to ½%
Phenol ¼% to ½%
(combined antipruritics)
and/or
Solution of coal tar 5% to 20%
(as "reducing, antieczematous, and antipruritic agent)
and/or

(as of December, 1958) †

Product	Concentration of Corticosteroid	Other Active Ingredients	Vehicle	Quantities and Containers
		Group I—Hydrocortisone Only		
Cort Dome Creme	0.25, 0.5, 1, and 2%	None	Acid Mantle Creme	½, 1, 4, and 16 oz jars
Cort Dome Lotion	0.5, 1, and 2%	None	Acid Mantle Lotion	½, 1, and 4 oz plastic squeeze bottles
Cortef Acetate Ointment	1 and 2.5%	None	Ointment	5 and 20 Gm tubes
Cortifan Cream 1%	1%	None	Water washable cream	10 Gm tube
Cort spray	0.5%	None	Liquid	15 ml squeeze spray bottle
Cortril Acetate Topical Ointment	1 and 2.5%	None	Ointment	5 and 15 Gm tubes
Hydrocortisone Acetate Ointment	1 and 2.5%	None	Ointment	5 and 20 Gm tubes
Hycortole Cream	1 and 2.5%	None	Cream	5 and 15 Gm tubes
Hycortole Lotion	1%	None	Lotion	15 ml bottle
Hycortole Ointment	1 and 2.5%	None	Ointment	5 and 15 Gm tubes
Hydrocortone Acetate Topical Ointment	1 and 2.5%	None	Zinc stearate, polyethylene glycol, propylene glycol water ointment	5, 15, and 30 Gm tubes
Hydrocortone Topical Lotion	0.5, 1, and 2.5%	None	Lotion	15 ml plastic bottle
Topicort Ointment	1 and 2.5%	None	Ointment	5 and 20 Gm tubes
Topicort Spray	0.5%	None	Lotion	15 ml aerosol spray
		Group II—Hydrocortisone Plus Other Active Agents		
Acne Cort Dome Creme	0.25%	4% sulfur 1% thiobis (4, 6 dichlorophenol), 3% resorcinol monoacetate	Acid Mantle Creme	1 oz tube
Acne Cort Dome Lotion	0.25%	4% sulfur 1% thiobis (4, 6 dichlorophenol), 3% resorcinol monoacetate	Acid Mantle Lotion	1 oz plastic squeeze bottle
Achrocort	1%	3% tetracycline hydrochloride	Water-washable cream	5 Gm tube

℞
Crude coal tar 10% to 20%
Tween 20 05%
Ointment of zinc oxide ad 300
S Water washable crude coal tar ointment, apply [illegible]
[illegible]
tion)

A great variety of modified tar preparations is commercially available and may present advantages where ordinary coal tar cannot be used, eg, Tarbonis Cream and Kolpix

℞
Solution of coal tar 100
S Tar solution—paint on affected areas one or more times daily
(N B In torpid, very thickened, circumscribed, lichenified areas the coal tar solution can be painted on the thickened sites, covered immediately with adhesive tape (eg, Elastoplast), left in place for 2, 3, or more days and then removed and freshly applied This procedure can be repeated as often as required)

℞
Vioform ointment
or
Vioform cream
or
Sterosan ointment
or
Sterosan cream
S Apply to affected parts 2 or more times daily and bandage on as required

The above preparations are particularly useful in secondarily impetiginized or otherwise infected "eczemas" and especially in "eczemas" of certain sites such as the hands and feet (eg, "housewives eczemas," "dishpan hands," dysidrotic eczemas, "pustular bacterids," recalcitrant vesiculopustular and scaly eruptions of the hands and feet, and otitis externa) The ointments are generally less drying and better tolerated where lubrication is desired *Combinations* of these quinoline derivatives as well as of coal tar *with hydrocortisone*, are among the most effective and modern of local remedies and have a wide range of usefulness in a great variety of eczematous and eczematoid eruptions (see prescriptions given on page 745)

For Both Acute and Chronic Forms and for Special Sites —*Topical steroids* have been proved to be perhaps the most versatile and effective of external remedies developed for dermatologic therapy One of the newest of these compounds triamcinolone acetonide (Kenalog or Aristocort acetonide), has in our hands shown superior effectiveness in most cases of inflammatory dermatoses responsive to any form of topical steroid therapy

There have been no reported systemic ill effects from any of the topical steroids except fludrohydrocortisone (occasional sodium chloride and water retention) In our hands topical steroid preparations have been proved entirely safe for widespread applications in the management of even the most extensive and long lasting dermatoses Moreover, there have been no reported instances of local

Table 53—Cont'd

Product	*Concentration of Corticosteroid*	*Other Active Ingredients*	*Vehicle*	*Quantities and Containers*
Hydroderm Ointment	1 and 2.5%	0.35% neomycin base, 1,000 units zinc bacitracin per gram	Emollient base	5 and 15 Gm tubes
Hydro-Tar	0.5 and 1%	5.83% liquor carbonis detergens	Cream	15 Gm tube
Neo Cort Dome Creme	0.5 and 1%	0.5% neomycin sulfate	Modified Acid Mantle Creme	½, 1, and 4 oz tubes
Neo-Cort Dome Lotion	0.5 and 1%	0.5% neomycin sulfate	Acid Mantle Lotion	½, 1, and 4 oz plastic squeeze bottles
Neo Cortef Cream	1 and 2.5%	0.5% neomycin sulfate	Cream	5 Gm tube
Neo Cortef Lotion 1%	1%	0.5% neomycin	Lotion	15 and 30 ml plastic bottles
Neo Cortef Ointment	0.5, 1, and 2.5%	0.5% neomycin sulfate	Ointment	5 and 20 Gm tubes
Neopolycin HC Ointment	1%	Neomycin sulfate 3 mg, bacitracin 400 units, polymyxin B sulfate 8,000 units per gram	Fuzene Ointment	5 Gm tube
Neo Resulin F	0.5%	1.5% resorcinol monoacetate, 2.0% sulfur, 0.5% neomycin sulfate	Cream	15 Gm tube
Neo-Tarcortin Ointment	0.5%	0.35% neomycin sulfate, 5.0% coal tar extract (Tarbonis)	Hydrophilic vanishing cream	7 Gm and 1 oz. tubes
Pantho F Cream	0.2 and 1%	2% pantothenylol	Water miscible cream	0.2% in 5, 15, and 20 Gm and 2 oz tubes and 1 lb jars; 1% in 5 and 20 Gm tubes
Resulin F Cream	0.5%	1.5% resorcinol monoacetate, 2% sulfur	Cream	15 Gm tube
Selsunef Ointment	0.5%	0.5% selenium disulfide	Soft petrolatum	5 Gm tube
Sterosan Hydrocortisone Ointment and Cream	1%	3% 5, 7-dichloro 8 hydroxy-quinaldine	Ointment or cream	5 Gm tube
Supertah 5	1%	Supertah (a concentrate of crude coal tar) equivalent to 5% crude coal tar	Washable base	½ oz jar

Achromycin Ointment 3% with Hydrocortisone 2%	2%	3% tetracycline hydrochloride	Ointment	5 Gm tube
Bacimycin with Hydrocortisone 1%	1%	0.5% neomycin, 500 units bacitracin per gram	Ointment	⅛ oz tube
Bur Cort	0.25, 0.5, and 1%	None	Burow's emulsion	½, 1, and 2 oz plastic bottles
Caldecort	1%	3% calcium undecylenate 0.5% neomycin sulfate	Water washable ointment	7 Gm tube
Cort Acne Lotion	0.25%	8.5% n sulfanilyacetamide, 2% resorcinol, 5% colloidal sulfur	Flesh colored greaseless lotion	1 oz bottle
Cor Tar Quin Creme	0.5 and 1%	2% solution of coal tar U.S.P., 1% diiodohydroxyquinoline U.S.P.	Acid Mantle Creme	½, 1 and 4 oz tubes
Cor Tar Quin Lotion	0.5 and 1%	2% solution of coal tar U.S.P., 1% diiodohydroxyquinoline U.S.P.	Lotion	15, 30, and 120 ml plastic bottles
Cortisporin Ointment	1%	5,000 units molymyxin B sulfate, 400 units bacitracin, 5 mg neomycin per gram	Petrolatum	½ oz tube
Cort Quin Creme	0.5 and 1%	1% diiodohydroxyquinoline	Cream	15 and 30 Gm tubes
Cortomycin	1 and 2.5%	0.5% neomycin sulfate	Ointment	15 and 20 Gm tubes
Epiderm ap Creme	0.5%	2% salicylic acid, 1% iodochlorhydroxyquin, ¼% menthol	Cream	15 and 20 Gm tubes
Es A Cort Creme	0.5 and 1%	56,000 I.U. estrone per ounce 100,000 U.S.P. units Vitamin A per ounce	Acid Mantle Creme	15 Gm tube
Hist A Cort E	0.5 and 1%	100,000 units synthetic vitamin A and 56,000 I.U. estrone per ounce, 2% pyrilamine maleate	Acid Mantle Creme	½ and 1 oz tubes
Hydrobalm Topical Cream	0.5%	3% benzocaine, 0.05% hexylated metacresol	Water washable fleshtone calamine cream	5, 15, and 30 Gm tubes
Hydrobalm Topical Lotion	0.5%	3% benzocaine, 0.05% hexylated metacresol	Water washable fleshtone calamine lotion	15 and 30 ml plastic bottles

(Table 53 continued on pages 742 744.)

Table 53—Cont'd

Product	*Concentration of Corticosteroid*	*Other Active Ingredients*	*Vehicle*	*Quantities and Containers*
		Group IV—Fludrocortisone		
Alflorone Acetate Lotion	0.1 and 0.25%	None	Lotion	15 ml plastic bottle
Alflorone Acetate Ointment	0.1 and 0.25%	None	Emollient base	5 and 15 Gm tubes
F Cortef Ointment	0.1 and 0.2%	None	Ointment	5 Gm tube
Florinef Lotion	0.05, 1, and 0.2%	None	Lotion	15 ml plastic squeeze *bottle*
Florinef Ointment	0.1 and 0.2%	None	Plastibase	5 and 20 Gm tubes
Florinef S Cream	0.1%	0.25% neomycin, 0.025% gramicidin	Cream	5 Gm tube
Florinef S Lotion	0.05 and 0.1%	0.25% neomycin, 0.025% gramicidin	Lotion	15 ml plastic squeeze bottle
Florinef S Ointment	0.1%	0.25% *neomycin, 0.025%* gramicidin	Plastibase	5 and 20 Gm tubes
Myconef Ointment	0.1%	0.25% neomycin, 0.025% gramicidin, 100 000 units nystatin per gram	Plastibase	15 Gm tube
		Group V—Hydrocortamate (Hydrocortisone Ethamate Hydrochloride)		
Magnacort Topical Ointment	0.5%	None	Ointment	1/6 and 1/2 oz tubes
Neo Magnacort Topical Ointment	0.5%	0.5% neomycin sulfate	Ointment	1/6 and 1/2 oz tubes
Aristocort Acetonide Cream	0.1%	None	Cream	5 and 15 Gm tubes
Kenalog Cream	0.1%	None	Cream	5 and 15 Gm tubes
Kenalog Ointment	0.1%	None	Ointment	*5 and 15 Gm tubes*
Kenalog Lotion	0.1%	None	Lotion	15 ml plastic squeeze bottle

*Based on Table I in Sulzberger, M B, Witten, V H, and Kopf, A W The Topical and Systemic Use of Corticosteroids in the Treatment of Skin Disease, Postgrad Med 24 379, 1958

†N B The number of topical preparations containing corticosteroids alone or in combination has continued to multiply at such a rate that it appears inexpedient to attempt to tabulate all the new items and combinations, which add few if any therapeutic advantages over those listed in this table which is complete to 1959 However it should be mentioned that two new groups of compounds have been added to the available topical corticosteroid preparations fluorometholone (Oxylone Cream and Neo Oxylone Ointment) and dexamethasone (Neo Decadron Cream)

Tarcortin Ointment	0.5%	5% coal tar extract	Hydrophilic vanishing cream	7 Gm. and 1 oz tubes
Tarcortin Lotion	0.5%	5% coal tar extract	Lotion	15 ml plastic squeeze bottle
Terra Cortril Ointment	1%	3% terramycin	Ointment	5 and 15 Gm tubes
Vioform Hydrocortisone Cream	1%	3% Vioform	Cream	5 and 20 Gm tubes
Vioform Hydrocortisone Lotion	1%	3% Vioform	Water washable lotion	15 ml plastic squeeze bottle
Zetone Cream	0.25%	1% Zetar	Vanishing cream base	1 oz jar
Zetone Lotion	0.25%	1% Zetar	Flesh colored greaseless lotion	30 ml bottle
Group III—Prednisolone and Prednisolone 21 Phosphate				
Hydeltracin Topical Lotion	0.5% prednisolone	0.5% neomycin	Lotion	15 ml plastic squeeze bottle
Hydeltrasol Lotion	0.5% prednisolone 21 phosphate (as sodium salt)	None	Lotion	15 ml plastic squeeze bottle
Hydeltrasol Ointment	0.5% prednisolone 21 phosphate (as sodium salt)	None	Ointment	5 Gm tube
Meti Derm Aerosol	0.3% prednisolone (a 3 second spray delivers approximately 0.5 mg prednisolone)	None	Liquid	150 Gm. aerosol spray can
Meti Derm Cream	0.5% prednisolone	None	Water washable cream	10 and 25 Gm tubes
Meti Derm Ointment with Neomycin	0.5% prednisolone	0.5% neomycin	White petrolatum	10 and 25 Gm tubes
Neo Delta Cortef Lotion	0.5% prednisolone	0.5% neomycin sulfate	Lotion	15 ml bottle
Neo Delta Cortef Ointment Topical	0.5% prednisolone	0.5% neomycin sulfate	Ointment	5 and 20 Gm tubes
Neo-Hydeltrasol Lotion	0.5% prednisolone 21 phosphate (as sodium salt)	0.5% neomycin sulfate	Lotion	15 ml plastic squeeze bottle
Neo-Hydeltrasol Ointment	0.5% prednisolone 21 phosphate (as sodium salt)	0.5% neomycin sulfate	Ointment	5 Gm tube

(Table 53 continued on page 744)

EMOLLIENTS AND DEMULCENTS

This class of medicaments is used to make the skin surface supple and less 'dry' or scaly They do this by confining and preventing evaporation of the sensible and insensible perspiration and/or by supplying water (humectant action), colloids, oils, and greases to the horny layer and by softening and/or removing excess scales

℞
Rose water ointment
S Apply as often as required and especially after each washing or bathing

℞
Acid Mantle Creme
S As for first prescription

℞
Liquid mineral oil
S As for first prescription

℞
Lanolin or
Borofax
S As for first prescription

℞
White petrolatum
S As for first prescription

℞
Nivea oil
(Emulsion of cholesterol derivatives of lanolin)
S As for first prescription

℞
Lubriderm (unscented)
(Emulsion of cholesterol derivatives)
S As for first prescription

℞
Acid Mantle Lotion
S As for first prescription.

℞
Aveeno for the bath
[illegible]
S [illegible]
some protection]

℞
Linit starch (unscented)
(Hydrolyzed cornstarch)
S 1 pound to tubful of lukewarm water
[*Caution* As for preceding prescription]

℞
Glycerin and rose water lotion
'Lotio glycerini *
Glycerin
Rose water āā
S As for first prescription
[Especially useful for dry or chapped hands—probably because of humectant action of the proportions of glycerin and water]

*Pharmaceutical Recipe Book ed 3 American Pharmaceutical *Association*, p 388 1943

irritation or allergic sensitization This remarkable efficacy and clinical record of safety, plus the lack of sting, stench, or stain, have made this drug one of choice as an antieczematous agent in practically all stages of "eczema," as an antipruritic and as a general anti inflammatory topical remedy Despite their present high cost to the patient, hydrocortisone or other topical steroids, alone or in combination with other topical agents, often prove themselves more economical than older remedies by virtue of the speedy relief afforded, sometimes by relatively small quantities However, topical steroids should not generally be relied upon *alone*, for they should never be regarded as specific or curative agents but rather as a *morbidistatic* ones Topical steroids, just like systemic ACTH or corticosteroid therapy, should be depended upon only to give relief while nature, either alone or together with the remedies prescribed by the physician, strives to effect the cure

R
Hydrocortisone free alcohol 1% to 2½%
Petrolatum ad 15 0
or
Hydrocortisone *1% to 2½%*
Hydrophilic ointment ad 15 0
S Apply by gentle massage two or more times daily
R
Hydrocortisone lotions 1% to 2½%
S Apply to affected parts 2 or more times daily

[Proprietary lotions containing 1 to 2½ per cent hydrocortisone as the free alcohol or acetate are available as proprietaries manufactured by many reliable pharmaceutical houses (See Table 53)]

Especially in widespread dermatoses, these lotions are sometimes more economical and effective than the ointments or creams, as they can be more rapidly applied and evenly spread in a thin film over large skin areas

COMBINATIONS OF TOPICAL HYDROCORTISONE WITH CRUDE COAL TAR AND DERIVATIVES —These are among the best antieczematous agents available They are marketed under a variety of names (See Table 53)

The following are particularly effective for eczematous or eczematoid eruptions in special areas, e g, hands, feet, anogenital regions, external ear and external ear canal, eyelids, labial and perioral areas, and for infected "eczemas" in general

R
Combinations of hydrocortisone with quinolines (See Table 53), e g,
Vioform ointment with
1% to 2½% hydrocortisone free alcohol
or
Vioform cream with
1% hydrocortisone
R

R Kenolog cream or Kenolog ointment or lotion

℞

Dihydroxyanthranol (Anthralin) ointments 0 1, 0 25, 0 5, and 1 0%

S Apply by gentle massage with finger covered by rubber finger cot, 1 to 3 times daily [Start with weaker concentrations and increase as required]

Modified Whitfield's Ointment

℞

Salicylic acid	0 9
Benzoic acid	1 8
Petrolatum	
Lanolin aā ad	30 0

S Rub into affected areas 2 or more times daily

Tincture of Benzoic and Salicylic Acid

℞

Salicylic acid	3 6
Benzoic acid	7 2
Alcohol ad	120 0

S Paint on affected areas 1 to 3 times daily and powder over with talcum or antimycotic powder [See following prescriptions]

℞

Resorcinol	3 0 to 6 0
Calamine lotion ad	100 0

S Paint on affected areas once to twice daily until desquamation occurs Then soothe with plain calamine lotion Repeat if and as necessary

℞

Salicylic acid	0 9 to 1 5
Sulfur precipitate	1 5 to 3 0
Ointment of zinc oxide	*30 0*

S Apply to affected areas once to twice daily

For prevention of recurrences and in managing mild cases of dermatophytosis of the feet and intertriginous areas, the application of preparations containing fatty acids (e g , propionic, undecylenic, and caprylic acid) is often useful Many proprietary preparations are available under various names Among those having quite general acceptance are Desenex powder, ointment, and tincture, Sopronol powder, ointment, and tincture, new Salundek ointment

An important feature of management is the prevention of skin damage by friction, sogginess, maceration, heat, and humidity, as these furnish the conditions for the rapid multiplication and developing pathogenicity of the fungi For this reason, the skin of intertriginous areas (beneath breasts, folds of the pendulous abdomen, intergluteal, inguinal and perivulvar folds, between toes, at the labial commissures, etc) should be kept dry and 'aerated' by every possible means such as, for example, soft cloths or lamb's wool wisps separating the toes aerated, perforated shoes, sandals, loose absorbent clothing scrupulous gentle drying after bathing, and the daily application of one of the fatty acid containing powders to the areas prone to fungous infection It can be predicted that topical therapy and depilation by x rays will be almost entirely superfluous when the griseofulvin safety and efficacy have been established in the treatment of the common fungous infections of the hair and nails The following descriptions of pre griseofulvin approaches will then be of historical rather than practical value When griseofulvin is given orally in doses of from 250 to 1,000 mg daily (the lower dose for smaller children), fungous infections of scalps will generally yield in a few weeks This

Since scaliness and dryness are often the result of either clinically observable or subclinical' inflammation, most of the milder measures recommended for eczematous dermatitis (page 738) will be found useful as emollients and demulcents in many cases of dry skin' Moreover, 'dry skin" is frequently a symptom of systemic changes which should be correctly treated when possible, e g, hormonal (thyroid) disturbances, nutritional defects senescence, and hereditary anomalies

ANTIFUNGAL AGENTS (Agents Used in Superficial Fungous Infections by Dermatophytes and Candidas [Monilias])

Dermatology deals mainly with the fungous infections of the glabrous skin, hair, and nails by the dermatotropic fungi known as dermatophytes and by *Candida albicans* This section is confined to the presentation of the drugs of choice in these particular infections which are today generally called dermatophytosis and candidiasis or moniliasis

Infections of the Glabrous Skin by Dermatophytes—A new oral antibiotic, griseofulvin (Fulvicin, Grifulvin), is now showing remarkable promise in the treatment of all forms of dermatophytic infections of the skin, hair, and nails Following the report of Gentles' studies on guinea pigs and according to the now numerous published clinical reports the administration by mouth of 1 to 2 Gm per day is generally well tolerated and usually leads to clinical clearing of most of the skin lesions in a few weeks If this *Penicillium* derivative lives up to only a part of its *early spectacular promise it will represent a drug of choice for microsporon infec*tions including those of children s scalps and all trichophyton infections including athlete s foot, etc There are also reports of its efficacy in certain deep mycoses notably those due to *Nocardia brasiliensis* (Latapi and co workers)

However, there are still many unknowns concerning this antifungal antibiotic including its long term toxicity, its allergenic potentials, the recurrence rate and reinfection rate after treatment, whether or not or when it is advantageous to combine the administration of internal antibiotics with the older external remedies, etc

For these reasons among others, the old established forms of treatment are at this moment still indispensable and are here described

The main old established therapeutic mechanism in dealing with these is the peeling off or other removal of the horny layer, soggy macerated skin surface, or horny structures which harbor the massive colonies of the causal fungi, combined with a surface fungicidal or fungistatic effect which prevents the spread of the colonies and invasion of new areas The following are among the most useful preparations for these purposes

℞
Dilute tincture of iodine
Tincture of iodine 1 part
Alcohol 6 parts
S Dab on affected areas twice daily
Powder over with talcum

℞
Ammoniated mercury ointment
S Apply to affected areas by gentle massage 2 to 3 times daily

℞
Dihydroxyanthranol (Anthralin)
ointments 0 1, 0 25, 0 5, and 1 0%
S Apply by gentle massage with finger covered by rubber finger cot 1 to 3 times daily [Start with weaker concentrations and increase as required]

Modified Whitfield s Ointment

℞

Salicylic acid		0 9
Benzoic acid		1 8
Petrolatum		
Lanolin aa	ad	30 0

S Rub into affected areas 2 or more times daily

Tincture of Benzoic and Salicylic Acid

℞

Salicylic acid		3 6
Benzoic acid		7 2
Alcohol	ad	120 0

S Paint on affected areas 1 to 3 times daily and powder over with talcum or antimycotic powder [See following prescriptions]

℞

Resorcinol		3 0 to 6 0
Calamine lotion	ad	100 0

S Paint on affected areas once to twice daily until desquamation occurs Then soothe with plain calamine lotion Repeat if and as necessary

℞

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holds true for favus and *Trichophyton tonsurans* infections as well as for those due to other trichophytons and microsporons Fungous infections of the nails generally yield more slowly and it can take several months before the affected nails are replaced by normal structures Unfortunately *Candida albicans* infections resist griseofulvin therapy and may indeed be made worse by it The duration of cure and the incidence of recurrence and/or reinfection are not yet known

External Treatment of Fungous Infections of the Hairy Scalp—This section will deal only with the common mycotic infections of the hairy scalp in children as caused in our geographic region by the two most frequently encountered species of Microsporum fungi namely *M audouini* and *M lanosum* In order to treat these safely and correctly it is imperative that the precise species of the infecting fungus be established by examination and culture from the hairs. If the microorganism is *M audouini* and the child is well below the age of puberty only x ray epilation by established dermatologic procedures will prove a safe and regularly effective external method

If on the other hand the infecting organism is a *M lanosum* or other zoophilic fungus caught from a cat or dog or other animal and is not the very refractory anthropophilic *M audouini* careful repeated daily external applications and vigorous shampooing will often lead to a cure Preparations such as those listed above under fungous infections of the glabrous skin and especially the tincture of iodine and the mercurial ointment applied alternately or Salundek used assiduously, are among the drugs of choice Very often the local applications and shampooing must be carried out to the point of slightly increased local irritation in order for the desired result to be achieved It is probable that just as in the case of the cure of fungous infections of the glabrous skin the main therapeutic effect is achieved through ridding the tissues of the masses of growing fungi by means of the actual removal of the infected hairs and other horny material itself together with the simultaneous prevention of the spread of the infection to new structures and areas by the surface presence of antifungal drugs

Whether oral griseofulvin or external therapy is used to prevent recurrences and to be sure of permanent cure the freedom of the scalp from infected hairs must be assured by regular routine examinations under the dark ultraviolet or Wood's light and when necessary by microscopic and cultural examination of suspected hairs

External Treatment of Fungous Infections of the Nails—Generally mild fungous infections of the nails which are causing no marked disfigurement and no cutaneous disease are best left untreated This applies especially to toenails for the infection is so very common and generally innocuous that it is best to let sleeping dogs lie

When nails are to be treated by topical measures the first principle of removing the horny material which contains the masses of fungous colonies still applies (see page 747 This can be done by dermatosurgical measures which range from complete surgical avulsion of the affected nails (a method usually necessary when the infecting fungus is a *Trichophyton purpureum*) to daily scraping off of the infected surface material with the edge of a glass slide, with an abrasive stone or with a dental burr Whatever the method of removal, one of the antifungal

medicaments listed above in the section on treatment of the glabrous skin should be applied regularly before and after the removal of the infected masses of keratin and, if possible, bandaged on at night

The *not uncommon accompanying paronychias must* be treated by systemic measures, hot soaks, and topical medicaments designed to allay the inflammation and combat the pyogenic as well as the fungal pathogens For these purposes the following prescriptions are useful

℞
Vioform and hydrocortisone cream

℞
Sterosan and hydrocortisone cream

℞
Mycostatin ointment

℞
Neosporin ointment

Monilial Infections —As stated, griseofulvin appears to be entirely ineffective against monilial infections This is particularly unfortunate because among the most common fungous infections of the skin and nails are those caused by *Candida albicans*—formerly known as *Monilia albicans* It is often difficult to establish the causal significance of this fungus even when present, as it is among the common nonpathogenic skin saprophytes and may grow exuberantly whenever the skin is damaged by other causes and is kept moist, macerated, and warm. Therefore, moniliasis is most likely to occur in the large skin folds in the intergluteal and ano genital areas at the angles of the mouth (perleche) and around the fingernails (paronychia) and in "wet workers" It is also likely to occur in obese persons and in those with diabetes

In addition to the antifungal measures described in the section on Dermatophytes, the following prescriptions are of antimonilial value

Gentian Violet Solution

℞

Methylrosaniline chloride	0 6
Alcohol	6 0
Distilled water q s ad	60 0

S Paint on affected areas 2 to 3 times daily and powder over with antifungal powder (see *previous section*)

[N B Stains can be removed from skin with aromatic spirits of ammonia, and from clothing by washing with sodium carbonate, soap and water]

℞
Mycostatin ointment or powder
S Apply to affected areas 2 to 3 times daily

Often the control or elimination of contributory and predisposing factors takes on even more importance than direct antifungal therapy These include the control of diabetes, obesity, hyperhidrosis, macerating occupational and other exposures, reduction of the occlusive and frictional effects of clothing and footgear, and oral hygiene and dental correction of malocclusion

At present it is of utmost importance to recall that overgrowth of monilias *and resultant moniliasis is today not infrequently the consequence of destruction*

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℞

Salicylic acid	5% to 15%
Petrolatum ad	30 0

S Apply once or several times daily to areas to be peeled

℞

Salicylic acid plaster (on moleskin adhesive)	40%

S Cut to fit area to be peeled, apply and leave in place 24 to 72 hours Remove, clean away macerated horny material, and reapply plaster as often as required

℞

Benzoic and salicylic acid ointment (modified Whitfield s ointment)

S Apply one or more times daily until desired peeling sets in—then apply soothing remedies

[Especially useful in fungous infections of the feet, etc.]

℞

Resorcinol		3% to 6%
Zinc oxide		
Talc	aa	15 0
Glycerin		10 0
Water		
Alcohol	aa	40 0

S Apply one or more times daily until desired peeling sets in. Then soothe

[Especially useful in superficial fungous infections of the groins and other intertriginous areas]

℞

Salicylic acid collodion

S Apply to corn or callus as required until peeling sets in

[Especially useful in treating corns]

℞

Salicylic acid	10 0
Diachylon ointment ad	100 0

Lead Oleate Plaster

℞

Lead monoxide	1000 0
Olive oil	1000 0
Lard	1000 0
Water q s	

Diachylon Ointment

℞

Lead oleate plaster	50 0
Lavender oil	1 0
White petrolatum	49 0

S Rub into hyperkeratotic thickened skin areas with a soft nailbrush or toothbrush one or more times daily

[Especially useful in hyperkeratotic lesions of palms and soles Do not rub into large denuded areas as lead poisoning may result]

N B See also the topical remedies given for acne (page 729), and for superficial fungous infections (page 747), since these too act mostly by virtue of their keratolytic effects

of other competitive microorganisms by antibiotic drugs Therefore in all cases of moniliasis this causal mechanism should be sought and eliminated whenever possible

AGENTS USED IN INFESTATIONS (Antiscabietic and Antilouse Drugs)

The older sulfur containing salves, delousing turpentine, mercurials, and oils have been almost completely replaced by the following modern drugs of choice

℞
Gamma benzene hexachloride ointment 60 0
S [illegible]
For Pediculosis—Apply directly to all the in [illegible]

℞
Crotamiton cream (Eurax) 20 0 to 60 0 Gm
S *As above*

℞
Benzyl benzoate chlorophenothane lotion 120
(Topocide a mixture of D D T benzyl benzoate, and benzocaine)
S Apply evenly to entire body from neck down after taking a warm soap-and water bath and drying thoroughly Massage in carefully to predisposed areas such as wrists between fingers around nipples on axillary folds Do not get into eyes[1] Leave on for 24 hours then take a warm soapy bath again and change to all clean freshly washed bedclothes under clothes and if possible dry cleaned outer garments [Have all members of family and other contacting persons examined by doctor and treated if necessary]

Lice and nits of the eyelash area are best treated with ophthalmic yellow oxide of mercury ointment

KERATOLYTICS

Keratolytics are used to remove excess horny material or keratin—as in treating calluses corns scaliness, hyperkeratotic and superficial fungous infections hyperkeratotic plugs in acne etc Since these agents act not by *lysis* or dissolving of keratin but by producing desquamation, only time-honored custom justifies retention of the designation keratolytics" rather than that of desquamating agents" or peeling agents for this class of drugs

lupus erythematosus like skin changes, exfoliative dermatitis, ophthalmic disorders and blood dyscrasias) Regular complete examinations, including dermatologic inspections blood counts, and examinations for disturbances of visual accommodation, are essential while patients are taking the above drugs

In addition to the systemic medication, all measures to protect the skin against great or prolonged exposures to sunlight and artificial ultraviolet rays are indicated For, while not all cases of discoid lupus erythematosus are manifestly harmed by exposures to light, spread of the eruption, exacerbation and transformation into subacute or acute disseminated forms are not altogether unusual following exposures to sun or ultraviolet rays

The chemical and physical sun screening preparations are therefore among the drugs to be used in lupus erythematosus (See section on 'Sun Screens," page 771)

Acute Disseminated (Systemic) Lupus Erythematosus —The treatment of acute disseminated lupus erythematosus is in many ways similar to that of pemphigus, at least in so far as the use of morbidistatic doses of corticosteroids and/or ACTH is concerned (See section on Bullous Dermatoses page 732)

In addition, the administration of the antimalarials, somewhat as used in chronic discoid lupus erythematosus, is today believed by many authorities to be of value Other authorities believe these antimalarials to be dangerous and strictly contraindicated in acute systemic lupus erythematosus It is my impression that the ill effects observed by some who used the antimalarials may be based on mechanisms similar to those of the Herxheimer reaction in syphilis, and that these may be *avoided or reduced* by starting with very small doses of antimalarials and by the *concomitant steroid* therapy

I usually give the antimalarials simultaneously with the corticosteroids, but often (and especially at the beginning) in much smaller doses than those employed in chronic discoid lupus erythematosus

A most important feature in prolonging the lives of patients with acute disseminated lupus erythematosus is the forestalling and/or treatment of such dire manifestations and complications as pleurisy and other pulmonary disease, pericarditis and other cardiopathy, and especially renal disease and renal failure by the indicated anti infectious dietary, and supportive measures

Subacute Disseminated Lupus Erythematosus —The nosology of this form places it between the chronic discoid form of lupus erythematosus and the acute disseminated form Treatment is essentially along the lines of both these forms with special emphasis on avoiding or combating stresses which can lead to the transition into the acute disseminated form Prominent among these stresses are various intercurrent infections exposure to cold heat, and particularly light All measures to protect against these must be scrupulously and persistently carried through (See section on Sun Screens" page 771)

ANTIPERSPIRANTS (*Agents Used in Hyperhidrosis*)

Hyperhidrosis or excessive sweating and faulty delivery and composition of the sweat are contributory factors which can be of great importance in such dermatoses as fungous infections (*dermatophytosis moniliasis* of the skin), eczema

AGENTS USED IN LICHEN PLANUS

There are no drugs which are regularly effective in past arsenic and bismuth have been considered as the most ures Corticosteroids and recently especially triamcinolon therapy, remain the measures most frequently employed

Antipruritic measures (page 757) are often required in eczematous dermatitis (page 738) are also indicated stage, and site of the lesions (e g , thickened, hyperkeratot hyperkeratotic plaques intralesional injections of hydrocortis effective corticosteroids are often beneficial

AGENTS USED IN LUPUS ERYTHEMATOSUS

At least three clearly recognizable forms of disease n erythematosus in their designations (1) chronic discoid lu acute disseminated lupus erythematosus (also today som *lupus erythematosus)*, and (3) subacute disseminated lupus

It is probable that these three designations apply to di and degrees of the same syndrome, and there are undeniabl evidence of transition from one form to another

However, the therapy of the different forms differs an at all similar Discoid lupus erythematosus generally is an mainly cosmetic implications, acute disseminated lupus ery fatal unless kept under constant adequate morbidistatic tr seminated lupus erythematosus is a very serious disease, acute form The differential diagnosis rests on clinical obs upon the presence or absence of the L E factor" and the tion of the "L E. phenomenon' in the blood

Chronic Discoid Lupus Erythematosus.—The older dr day been almost entirely replaced by the antimalarial quinc in rare refractory cases will the specialist still be forced to r of gold, bismuth, and other drugs which were routine until following are representative of the present drugs of choic

℞
Quinacrine hydrochloride tablets 1
S 1 to 2 tablets daily

℞
Chloroquine phosphate tablets 2
S 1 tablet daily for first few days If tolera crease dose to 2 or 3 tablets daily Continue as tolerated and for some time after skin have become inactive

Triquin

℞
Atabrine (quinacrine) HCl 25 n

Among the drugs to be used symptomatically and systemically in controlling hyperhidrosis of the palms and soles in particular, but of other body areas as well are the potent anticholinergic drugs like Banthine or Pro Banthine

When anticholinergics are given, the side effects such as *blurring of vision* difficulty of urination, and dryness of the mouth are the limiting factors, and very often the dose which will control the hyperhidrosis is the same as that which begins to *produce such side effects*

Ephedrine atropine, ergotamine tartrate, and barbiturates are among the older drugs which are sometimes useful in controlling nervous and emotional hyper hidrosis, in particular, and some other forms as well Combinations of these are common

Here again the *limiting factors are the side effects of dryness of the mouth* dilatation of the pupil, etc , which are produced by doses usually very close to those necessary to bring about a reduction of sweating

One of the best specialistic procedures for managing *certain* forms of *localized* hyperhidrosis is a course of properly administered and safely dosed x radiations This is not only the domain of the experienced specialist but also outside the scope of this book on drugs

PIGMENT PROMOTING AGENTS

Too little pigment in certain skin areas can be fully as disfiguring as too much pigment Loss of pigment, as in vitiligo or leukoderma probably brings a greater number of patients to the doctor than does excessive pigmentation

The internal or systemic or other cause can be discovered in only a small pro portion of cases e g , in syphilitic or psoriatic *leukodermas in loss of pigment due* to dietary and vitamin B deficiencies, to hormonal disturbances, in achromia para sitaria due to fungi, or in pigment loss caused by exposures to external agents such as rubber articles and medicaments containing hydroquinones, etc Therefore in most cases of vitiligo and other disfiguring loss of pigment, the treatment cannot be causal but remains symptomatic As of today the treatment of skin areas with too little pigment is quite as inadequate and unsatisfactory as the treatment of hyper pigmentation (See section on Bleaches page 731)

However, the oral administration of 8 methoxypsoralen (methoxsalen, Ox soralen) combined with exposure to natural sunlight or, when sunlight is not avail able to ultraviolet lamps, will bring about repigmentation in a certain proportion *of the properly treated cases* Cosmetically fairly satisfactory repigmentation in about 1 case in 7 is the figure obtained by us in the series of patients treated at the Skin and Cancer Unit of New York University Hospital

The repigmentation obtained is not necessarily *lasting* *It may remain* only a few weeks, but sometimes lasts up to several years without requiring retreatment Not only does the larger number of cases fail to respond, but even in responsive cases some areas are likely to remain refractory *Particularly the hands and the* genitalia are notorious for their lack of pigmentary response, but any skin areas can prove to be unyielding

tous and eczematoid eruptions dyshidrosis of hands and feet intertrigos, prickl heat, etc The control of hyperhidrosis is therefore an important medical matter as well as being of generally recognized esthetic and cosmetic importance in our society

Almost all of the purchasable antiperspirants are effective in moderate degrees of axillary sweating and are relatively safe—as attested by their daily use by tens of millions of persons They are almost all based upon their content of aluminum salts including aluminum chloride and aluminum chlorhydroxide as the simplest representatives

On occasion, however the preparations containing these salts produce allergic contact dermatitis or primary irritant dermatitis and can contribute or actually cause abscesses of the large sweat glands and apocrine glands especially of the axillae In such cases they either cannot be used at all or can be used only spar ingly No very effective substitute for the aluminum salts has yet been found However, considerable control of the axillary odors can be achieved by using prep arations containing antibiotics such as neomycin even without the antiperspirant aluminum salt Moreover the soaps containing good skin surface germicides such as Lifebuoy soap Dial soap and others are effective in controlling axillary odors for many hours and sometimes even days after their thorough use

A representative prescription of an antihidrotic lotion is the following

℞

Aluminum chloride	24 0
Dilute alcohol to make	100 0

S Dab on w th absorbent cotton as needed in cases of excessive sweating of palms soles or armpits

In hyperhidrosis of the feet the following powder has been found useful by our group

℞ *Medicated Foot Powder*

Sal cylic acid powder	2 0
Boric acid powder	6 0
Zinc stearate	3 0
Exsiccated alum	1 0
Starch	10 0
Purified talc to make	100 0

S Dust on 2 to 4 times daily as required

Foot baths with a 10 per cent solution of formaldehyde solution (37 per cent) ormalin) are also helpful in cases of excessive sweating of the feet

Even painting with the full strength formaldehyde solution (Formalin) may sed by the physician who has the necessary experience and judgment to apply material when indicated

When using formaldehyde in any form one must bear in mind the very h nce of contact type allergic dermatitis which the drug produces and be on okout for cases of hypersensitivity which are sometimes extreme in degree

Of course, in all forms of hyperhidrosis the underlying causes must be sought uminated where found Many cases are based upon nervous mechanisms and nal and psychic effects and the experienced skin specialist has learned how nguish between typical cases of these forms and others of different causation

causes, a great number of cases of generalized and localized itching remain unclarified as to causation The following medicaments are those of choice in the treatment of such idiopathic' pruritus They are also to be applied in pruritus of ascertainable etiology during the search for causes and while the reduction of causal mechanisms is being carried out and until causally directed measures bring complete relief

Topical Antipruritics—Often the medicaments listed under Antieczematous Agents (page 736) and simple Emollients and Demulcents (page 746) are also very effective and useful antipruritics (e g preparations containing tars medicated baths) Moreover, physical agents, such as applications of very hot or very cold water ethyl chloride spray, slapping etc, will often act as temporary antipruritics In addition for purely antipruritic effect are the following

℞
Menthol ¼% to 1%
and Phenol ⅛% to 1%
in Tinctures (e g, dilute alcohol, 50%)
or *Lotions* (e g, calamine lotion)
or Cold creams (e g, rose water ointment)
or Water washable creams (e g, hydrophilic ointment)

or

Antipruritic Powder

℞

Powdered camphor	4 5%
Menthol	0 5%
Zinc oxide	40 0
Talcum	45 0
Benzonite q s	100 0

S Dust on freely 3 or more times daily

[*N B* Particularly useful in itching intertrigo moniliasis, etc]

Local anesthetics as well as topical antihistaminics while often effective carry with them considerable risks because of their strong tendencies to sensitize and to produce (sometimes very severe) allergic dermatitis

Of all topical antipruritics topical *hydrocortisone* and derivatives are probably the safest and most generally effective, especially in thin skinned areas (eyelids ear canals scrotum genitalia in general, perianal region, etc)

Special types of pruritus and itching of particular sites often require special forms of local medication For example itching of the legs as found in association with the varicose or stasis complex is often best relieved by elastic stockings or Ace bandages or with some form of Unna's Zinc Gelatin Boot

One simple way to apply a zinc gelatin boot is to use a ready made form such as Dome Paste Bandage

Systemic Antipruritics—In addition to the elimination or medical or surgical treatment of all possible systemic causes of pruritus all the antihistaminic drugs (page 516) sedatives and tranquilizers (page 262) and soporifics (page 287) will have their indicated place in the relief of itching their selection must be made according to the type periodicity time and site of the itching and the particular requirements and responses of the individual case

Moreover, *systemic* administration of ACTH or of adrenocortical steroids have their distinct sphere of usefulness in managing acute self limited and severe cases

℞
Methoxsalen capsules or tablets 10 mg
S In children under 6, 1 tablet daily, in children over 6 and in adults, 2 tablets daily, followed in about 2 hours by exposure to sunlight or artificial ultraviolet in daily increments of gradually ascending amounts The light should be so dosed as to produce a slight erythema of depigmented spots

This form of treatment appears to be relatively safe Although it is tedious and time-consuming and difficult to carry out and is, as stated, ineffective in many cases and many areas, it is nevertheless the best available today Methoxsalen by the oral route is the drug of first choice, having almost entirely superseded the older more dangerous and less effective methods such as painting with liquefied phenol or the topical application of methoxsalen tinctures or solutions followed by exposures to light

Very recently, *dermabrasion* of vitiligo sites has been reported to be successful, but this *dermatosurgical* procedure falls outside the scope of this book on drugs

AGENTS USED IN PITYRIASIS ROSEA

This is usually a self-limited eruption Mild peeling measures such as the milder keratolytic lotions, oils, and creams see section on Keratolytics, page 751) and mild peeling with generalized ultraviolet light can be used to hasten the involution A useful prescription is

℞

Menthol	0 25
Resorcinol	3 0
Calamine lotion ad	100 0

There is usually pruritus varying from mild to very severe Its management relies on the measures detailed in the section on Antipruritics

Bathing and scrubbing with soap and particularly with one of the soaps containing surface active germicides (page 764 will be found useful in some cases In others, bathing and soaping prove irritating and bathing must be reduced and emollients or demulcents added to the bath water page 746)

ANTIPRURITICS (Agents Against Itching)

As stated in the discussion of antieczematous agents (see page 736) the causes of itching are manifold They may be external or internal or both In itching also it is obvious that the most effective therapy will be that which includes the discovery and reduction or elimination of the causal factors Therefore, in every case of protracted itching such internal causes as hepatic disease, blood dyscrasias, diabetes, gout, intestinal infestations drug sensitivities, endocrine disturbances, dietary and metabolic and psychic influences, and others must be sought for and appropriately treated when present Moreover, causal external factors, such as allergic and other reactions to contact agents (including insects, plants clothing topical medicaments, cosmetics, cleansers and occupational and household exposures) the varicose or stasis complex of the lower legs, the pruritic skin infections and infestations, and itching dermatoses, must be looked for and controlled when discovered However, even after the most expert and painstaking attempts to find and remove

causes, a great number of cases of generalized and localized itching remain unclarified as to causation The following medicaments are those of choice in the treatment of such "idiopathic" pruritus They are also to be applied in pruritus of ascertainable etiology during the search for causes and while the reduction of causal mechanisms is being carried out, and until causally directed measures bring complete relief

Topical Antipruritics —Often the medicaments listed under Antieczematous Agents (page 736) and simple Emollients and Demulcents (page 746) are also very effective and useful antipruritics (e g, preparations containing tars, medicated baths) Moreover, physical agents, such as applications of very hot or very cold water, ethyl chloride spray, slapping, etc, will often act as temporary antipruritics In addition, for purely antipruritic effect are the following

R
Menthol ⅛% to 1%
and Phenol ⅛% to 1%
in Tinctures (*e g, dilute alcohol, 50%*),
or Lotions (e g, calamine lotion),
or Cold creams (e g, rose water ointment),
or Water washable creams (e g, hydrophilic ointment)

or

Antipruritic Powder

R

Powdered camphor	4 5%
Menthol	0 5%
Zinc oxide	40 0
Talcum	45 0
Benzonite q s	100 0

S Dust on freely 3 or more times daily

[N B Particularly useful in itching intertrigo moniliasis, etc]

Local anesthetics, as well as topical antihistaminics, while often effective, carry with them considerable risks because of their strong tendencies to sensitize and to produce (sometimes very severe) allergic dermatitis

Of all topical antipruritics, topical *hydrocortisone* and derivatives are probably the safest and most generally effective, especially in thin skinned areas (eyelids, ear canals, scrotum, genitalia in general, perianal region, etc)

Special types of pruritus, and itching of particular sites often require special forms of local medication For example itching of the legs as found in association with the varicose or stasis complex is often best relieved by elastic stockings, or Ace bandages, or with some form of Unna's Zinc Gelatin Boot

One simple way to apply a zinc gelatin boot is to use a ready made form, such as Dome Paste Bandage

Systemic Antipruritics —In addition to the elimination or medical or surgical treatment of all possible systemic causes of pruritus, all the antihistaminic drugs (page 516), sedatives and tranquilizers (page 262), and soporifics (page 287) will have their indicated place in the relief of itching, their selection must be made according to the type, periodicity, time, and site of the itching and the particular requirements and responses of the individual case

Moreover, *systemic* administration of ACTH or of adrenocortical steroids have their distinct sphere of usefulness in managing acute self limited and severe cases,

as well as chronic very severe cases of itching, provided all other measures have failed Of course in administering these hormones all the necessary preliminary and concomitant examinations must be carried out and all the necessary caution and precautions observed

Many specialized and selected dermatologic physical procedures are also among the sovereign remedies for localized and generalized pruritus, e g , x ray grenz ray, thorium X, CO_2 slush localized peeling with caustics (page 735) and keratolytics (page 751)

Many systemic measures have been used in the attempt to allay pruritus None has been entirely satisfactory

Sedatives and soporifics while they may allay pruritus for a short time are not effective as a rule for the following reasons (1) because they very often produce sufficient drowsiness and sleepiness to make their employment dangerous or impossible during daytime working hours and (2) because while they may produce sleepiness and some disturbances of consciousness very often the scratch reflex will continue and patients will tear at their skin even more than if they were able to use conscious control to prevent scratching Thus one finds some patients scratching violently even in their sleep

While the antihistaminics in general have some antipruritic effect they are not universally useful to allay itching However by trial and error one will often find that in one patient or another a particular antihistaminic will be valuable in allaying pruritus Therefore each antihistaminic must be given a trial in each individual before one can say that none of this group of compounds will be of any use in a particular case Obviously where the pruritus is based upon an allergic mechanism as in certain cases of urticaria the antihistaminics may be useful in allaying the reaction of allergy itself

Although the so-called tranquilizers as a group are not very valuable in reducing the itch sensation itself there are individuals who will react very well to one or another member of the so called tranquilizer or ataractic group

Although these drugs as a group will not be discussed here since they have been included elsewhere in the text there is one that may deserve particular mention as a systemic antipruritic This is a phenothiazine derivative called trimeprazine (Temaril)

When originally tried out by our group the material was supplied in 5 mg 10 mg and 25 mg tablets These larger doses were sometimes effective in allaying pruritus but they were also often highly soporific and frequently left hang overs in the morning The dosage was then gradually reduced and at present Temaril is marketed in 2 5 mg units One two three or even four of these taken at night before retiring will be helpful in reducing the itching in a fair proportion of patients However in some patients even the smallest dose produces too much sleepiness and in many the drug cannot be taken during the day whereas in others even the larger doses are not effective in allaying the pruritus While this phenothiazine is sometimes a useful adjuvant in the systemic management of itching it is by no means the ideal drug and is not universally effective as was originally hoped Moreover there has been at least one well documented instance of a blood dyscrasia following its use

Other systemic measures for reducing itching include autohemotherapy, injections of calcium salts, and others

Of course, the best means of treating pruritus is to combat the basic pathologic mechanism which was the producing factor, e g, the elimination of contact and ingested or inhaled allergens, external irritants, intestinal parasites, insects, dyes, and causal allergenic drugs, and the management of diabetes, gout, liver disease, and blood dyscrasias

ANTIPSORIATICS (Agents Used in Psoriasis)

General Remarks —Psoriasis is a skin disease of entirely unknown cause, of very poorly understood pathogenic mechanism, and of very high incidence It has been estimated by some observers that, if one searches for and includes the very mildest cases, from 10 to 25 per cent of the adult white population of the United States may be affected at one time or another The disease can remain confined to one or a few scarcely noticeable small areas of slight scaling or it can be widespread or generalized and be completely incapacitating and refractory to all treatment The association with joint changes is much higher than can be accounted for by fortuitous coincidence In most patients and particularly in early mild forms, longer or shorter remissions of the skin eruption can be brought about by proper management In some fortunate patients the disease disappears after treatment or occasionally even without treatment, and the remission lasts for months, years, or even for the duration of the patient's life

The systemic treatment of psoriasis is largely unsatisfactory However, when *the patient is completely incapacitated or in dire distress, Aminopterin by mouth* or triamcinolone may be valuable after all else has failed According to a schedule of Rees B Rees, Aminopterin is given by mouth in doses of 0 5 mg *daily for 6* consecutive days, interrupted for 1 week, and resumed for 6 consecutive days Of course, the usual regular checkups for hematologic changes, oral lesions etc, *must* be rigorously carried

In addition to deliberate change of environment and climate (especially to dry, warm, even temperatured places), *local external measures* are the only regularly effective ones in psoriasis Among the best of these are such specialistic procedures as x rays, grenz rays, thorium X, various combinations of tar baths tar applications, and ultraviolet light exposures

Severe or widespread cases and chronic forms are usually nearly unmanageable except where there are specially trained personnel and specially equipped hospital facilities available for their care In many countries outside of the United States, such installations are available for the care of psoriatics, and many patients whose psoriasis remains refractory under haphazard and ambulatory treatment will respond to the proper applications carried out in special hospital areas skillfully, precisely, and patiently by devoted and experienced dermatologic nursing personnel

In the absence of the special dermatologic personnel and facilities in hospitals, the local medicaments listed below are often valuable in treating ambulatory patients with ordinary and not too widespread or inveterate psoriasis However here too, success is largely dependent upon the *way* in which the external medica

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tion is used, applied, and removed In many instances the medicaments are counterirritants and their therapeutic effects are very close to their irritant effects upon normal skin Thus it often occurs that the psoriatic patches do not begin to yield until there is some visible irritation of the normal skin around the patches which are being treated Usually the visible psoriatic lesions themselves and a narrow band of clinically apparently normal skin around them do not become irritated by concentrations and medicaments which irritate the rest of the patient's skin

General Directions —In torpid thickened lesions scrub off the scales with a soft brush or turkish washcloth while in a warm bath and before each application of medication Rub the local medication in thoroughly by gentle massage, either with the finger (rubber finger cot) or with a toothbrush or with a piece of pumice stone of suitable size, shape and abrasiveness

When the skin around the lesions begins to become reddened eczematized, swollen, or otherwise irritated, and in cases that are spreading or irritable or itchy or show signs of aggravation stop all the antipsoriatic remedies proper, and apply nothing but soothing medication as outlined under Antieczematous Agents (page 736) and Emollients and Demulcents (page 716) In soothing the skin which has been irritated by active antipsoriatic drugs the hydrocortisone-containing preparations are of outstanding value The antipsoriatic remedies can be started cautiously (perhaps in higher dilutions than before) after the skin irritation has subsided, but not until then

For the Scalp —
To remove scales

℞
Salicylic acid 2% to 3%
in
Olive oil
or
Mineral oil q s
S Apply 2, 3 or more times weekly to entire scalp, leave on overnight and wash out in morning

℞
Salicylic acid 3%
Triethanolamine 3%
Lubriderm (unscented) q s
S As in preceding prescription

℞
P & S Liquid
(Less than 2% phenol in sodium chloride solution)
S Shake well and apply to all scaly areas nightly

Helpful in removing scales, ointments, creams, etc, in psoriasis of scalp are the tar-containing shampoos, e g

℞
Almay tar shampoo
Zetar shampoo
Packer's tar shampoo, etc

(Fostex Cream shampoo can also be used, but not in combination with mercurials)

In addition, one of the following scalp oils and ointments should be applied nightly or as often as required and feasible

℞

Salicylic acid	3%
Ammoniated mercury	3% to 6%
Solution of coal tar	3% to 20%

[illegible]

S [illegible]
quired

(Beware of hypersensitivity, especially to mercurials *Do not combine* with sulfur containing applications)

℞

Salicylic acid	2%
Ammoniated mercury	3% to 6%
Solution of coal tar	6% to 10%
or	
Oil of cade	6% to 10%
Hydrophilic ointment	
or	
Hydrophilic petrolatum q s (or proprietary emulsion base or water washable base)	

S As for above prescription.

℞

Pyrogallic acid (pyrogallol)	3%
Salicylic acid	3%
in	
Hydrophilic petrolatum q s	

S Rub thoroughly into thickened scaly affected areas at night with a toothbrush or finger covered by finger cot

(Beware of irritations to eyes, do not get on face, remove from fingers after each application, do not use on light colored blond, gray, or white hair—will cause discoloration)

For superficial psoriasis of face, trunk, or extremities, the mercurial and tar preparations recommended for seborrheic dermatitis (page 766) may be the drugs of first choice When these fail or when the psoriatic plaques are thicker and inveterate, one of the following is chosen for trial

℞

Chrysarobin	0 25% to 5% or even 10%
Petrolatum	q s

(Must be freshly prepared)

S Rub thoroughly into affected areas 2 or more times daily Stop when skin around lesions becomes inflamed

(Do not use on face Beware of irritation of eyes, discoloration of hair, clothing bedding, etc)

℞

Chrysarobin	1% to 5%
Chloroform	q s

S Chrysarobin tincture—apply to affected areas 2 or more times daily, observing same precautions as for preceding prescription and in addition beware of excessive inhalation!

tion is used, applied, and removed In many instances the medicaments are counterirritants and their therapeutic effects are very close to their irritant effects upon normal skin Thus it often occurs that the psoriatic patches do not begin to yield until there is some visible irritation of the normal skin around the patches which are being treated Usually the visible psoriatic lesions themselves and a narrow band of clinically apparently normal skin around them do not become irritated by concentrations and medicaments which irritate the rest of the patient's skin

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P & S Liquid
(Less than 2% phenol in sodium chloride solution)
S Shake well and apply to all scaly areas nightly

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℞
Almay tar shampoo
Zetar shampoo
Packer's tar shampoo, etc.

[Fostex Cream shampoo can also be used, but not in combination with mercurials]

℞

Cignolin (Anthralin, in England, 'Dithranol')	0 4%
Salicylic acid	2 0%
Zinc oxide	25 0%
Starch	25 0%
Petrolatum q s ad	30 0 Gm

As stated at the outset, the local treatment of psoriasis can be highly satisfactory even in ambulatory patients, but the chances of success are incalculably greater where the adequate special personnel and institutional facilities are available and the patient can be intensively treated and closely observed

AGENTS USED IN PYODERMAS

Pyoderma is the inclusive term applied to skin infections by pyogenic microorganisms, principally staphylococci and/or streptococci Their management depends *mainly on the sites and depth of the infection, its distribution, and its course* (acute or chronic)

In general, the acute superficial pyodermas (e g , impetigo, folliculitis) can be treated by external measures The deeper pyodermas (e g , furuncles, carbuncles ecthyma cellulitis), particularly when chronic, usually require systemic therapy plus the external medicaments

Infections of the skin can still be adequately controlled by older medicaments The slow rate of absorption makes it possible to use as local external applications on skin infections many old established antibacterial agents which are much too toxic for systemic administration to combat infections of internal sites *These older remedies also have the great advantages of not contributing to the emergence of antibiotic resistant strains of staphylococci and other cocci and not producing hypersensitivity to useful antibiotics in the patients* Thus, the tremendous superiority of systemically administered sulfonamides and antibiotics over older systemic remedies for internal infections is not quite as marked in relation to the pyogenic infections of the skin

Among the older drugs of choice for superficial pyodermas are

℞
Compound Quinolor Ointment
(full strength or diluted equal parts with petrolatum) (See page 730)

℞
Vioform ointment

℞
Vioform cream

℞
Sterosan ointment

℞
Sterosan cream

℞
Ammoniated mercury ointment 30 0

℞

Sulfur precipitate	1 0 to 3 0
Salicylic acid	0 6 to 1 0
Ointment of zinc oxide ad	30 0

℞
D hydroxyanthranol (Anthral n) o ntments
0 1% 0 25% 0 5 % or 1 0%
Petrolatum q s 60 0
S Begin with weaker concentrat ons If tolerated work upward as requ red Precaut ons as w th chrysarob n o ntm ents

For widespread or generalized eruptions mercurial oils (see above) or Riasol are often the most practical and satisfactory local measures Tar containing baths are also of some use

A long time favorite and often the best treatment despite the difficult and time consuming nature of the procedure is the combination of applications of tar and daily exposures to ultraviolet light e g as follows

1 Soak in tar bath in evening before retiring brushing off scales while in tub

Examples

℞
Coal tar solut on 20 0
Polysorbate 80 5 0
Alcohol q s 100 0
S 4 tablespoonfuls to tub of water

or

℞
Almay Tar Bath
S As above

or

℞
Zetar emuls on
S 2 tablespoonfuls to the bath

2 Apply tar in one of the following forms to each of the lesions

℞
Solut on of coal tar

or

℞
Tar o ntment

or

℞
Crude coal tar 2% to 3%
Polysorbate 80 2% to 3%
in
O ntment of z nc ox de q s

3 Expose all the affected parts and the intervening skin to ultraviolet light* giving doses which are just below or just at the erythema producing level and con tinuing at this level by gradually raising the exposure time and/or decreasing the distance of source to skin in pace with the increasing skin tolerance

4 Repeat this treatment daily for as long as required unless the psoriasis spreads or the skin becomes irritated or other prohibitive ill effects appear

A modification of the above is the treatment with Cignolin paste as carried out for example in the antipsoriatic installation in Leeds England In this the application of the following paste confined precisely and absolutely to the visible psoriatic lesions and covered by bandages takes the place of the nightly tar ap plications

*Burd ck Hanovia Mercury Vapor Arc or West nghouse or General Electr c RS bulb

In the deeper pyodermas and even in the superficial persistent ones, systemic administration of penicillin and of other antibiotics is frequently indicated Penicillin can be given by injection, either in the aqueous or *repository vehicles, or it* can be administered by mouth For the newer oral penicillin preparations with forms for quicker absorption see page 141 Other antibiotics are given by mouth or by systemic injection as well

While giving the antibiotics for the protracted periods sometimes required to finally master a chronic or chronic recurrent pyoderma vitamin B complex should be administered concomitantly

In all pyodermas, and particularly in persistent or chronic recurrent ones, the first order of business is to search for, rule out, or treat underlying predisposing factors, including especially diabetes, blood dyscrasias, gout, dietary deficiencies, skin infestations, internal foci of infection, and pruritus from various causes

AGENTS USED IN SARCOIDOSIS

The treatment consists of all general medical measures directed against the multiform manifestations in the affected organs and sites Systemic treatment includes prolonged administration of corticosteroids, but in smaller doses than in pemphigus or acute/disseminated lupus erythematosus (See sections on Bullous Dermatoses and Lupus Erythematosus, pages 732 and 753)

ANTISEBORRHEICS

Among the main groups of standard topical remedies for seborrhea and seborrheic dermatitis are those containing mercury and those containing sulfur These are likely to be incompatible and should not be used together In each case the best tolerated and most effective should be chosen (as determined by the individual s response, allergic hypersensitivity, etc) The sulfur and the mercurial remedies are each generally employed in combination with other keratolytics, tars etc

Shampooing regularly is an essential of management of the scalp

Shampoos

℞
Medicinal soft soap liniment
or
shampoos containing hexachlorophene—e g , Dial shampoo pHisoHex, Gamophen
or
tar shampoos—e g , Almay tar, Zetar, etc
S Shampoo thoroughly one or more times weekly [When sulfur combinations are being prescribed locally, Fostex Cream shampoo can be used (This can be used also for washing face and other areas affected by seborrheic dermatitis)]

Sulfur-Containing Regimen for Scalp

℞

Sulfur precipitate		1 0 to 3 0
Salicylic acid		0 6 to 1 5
Solution of coal tar		1 5 to 3 0
Hydrophilic ointment	ad	30

℞

Resorcin	3 0 to 5 0
Sulfur precipitate	3 0 to 10 0
Zinc oxide	
Talcum	
Glycerin āā	15 0
Water	
Alcohol āā ad	100 0

One of the above ointments or creams or the lotion is selected according to the patient's sensitivities and previous responses and is applied to affected and surrounding areas 2 or more times daily by gentle massage or painted on with a flat brush [N B The mercury ointment should not be used over large areas or for prolonged periods unless the patient is under regular observation by the physician The main dangers are absorption and systemic toxicity—especially renal irritations—and particularly allergic sensitization and contact dermatitis]

Among the newer remedies are the mixed antibiotic-containing ointments, e g

℞ Neosporin ointment
℞ Bacitracin ointment
℞ Terramycin ointment
℞ Polysporin ointment
℞ Aureomycin ointment
℞ Achromycin ointment

These have the advantage of lack of irritancy relatively low sensitizing potential and low systemic toxicity, with a very wide antibacterial spectrum

The affected and surrounding areas should be washed with antiseptic-containing soaps or detergents Among these are the following

Mercurial soaps—e g Neko soap
or
Soaps containing hexachlorophene—e g , Dial soap pHisoHex,
or
Soaps containing tetramethyl thiuram disulfide (TMTD)—e g , Lifebuoy soap

Cleanliness of person (e g hands and fingernails) and cleanliness of clothing, bed linens, towels (regular washing with soap and hot water and regular cleansing of outer garments by dry cleaning or cleaning fluids) are essential to prevent reinfection, spread and continuation of the disease

In addition, daily "antiseptic' baths should be prescribed in all widespread or long-lasting pyodermas, e g , with potassium permanganate

℞
[illegible]
S [illegible]

Among the drugs of choice for deeper pyodermas are the above topical remedies plus continued hot, wet compresses with mild antiseptic solutions such as Burow's solution, e g

℞ Domeboro Powder
℞ Domeboro Tabs

These are especially useful in bringing abscesses, carbuncles, and furuncles to ripen, to "point," to open, and to drain

Mercury-Containing Regimen for Scalp

℞

Ammoniated mercury	1 0 to 4 5
Salicylic acid	0 6 to 1 5
Hydrophilic ointment ad	30 0

S Apply to scalp by thorough massage, leave on overnight and remove by any nonsulfur con taining shampoo

Mercury-Containing Regimen for Face and Trunk

℞

Ammoniated mercury	1 8
Bismuth subn trate	*1 8*
Zinc oxide	1 8
Talcum	1 8
Lanolin	
Petrolatum aā ad	30 0

S Test for 48 hours by applying several times to a small area of normal skin (about the size of a 50-cent piece) If no untoward react on en sues, apply to affected areas of face, trunk, etc., two or more times daily

Newer Preparations

Newer forms of management include the following and are particularly useful when the standard approaches with sulfur or mercury are not tolerated or prove ineffective

℞

Vioform cream

S Apply to affected parts 2 or more times daily

℞

Vioform cream with hydrocortisone

or

Sterosan cream with hydrocortisone

S Apply to affected parts 2 or more times daily

Combinations of hydrocortisone and antibiotics—e g

℞

Neo-Cortef ointment 1% to 2½%

or

Terra Cortril ointment etc

S Apply to affected areas 2 or more times daily

Combinations of tar and hydrocortisone—e g

℞

Solution of coal tar	1 2
Hydrocortisone free alcohol	0 1
Hydrophilic ointment ad	20 0

Tar containing properties, as well as those with added hydrocortisone and/or quinolines, can often be advantageous despite their usually substantially higher cost—e g

℞

TarCortin cream

or

℞

Cor Tar Quin

In addition to the listed topical agents, highly irritated forms of seborrheic dermatitis will often require preliminary treatment with the soothing applications

S Apply to scalp by thorough massage leave on overnight and shampoo out with Fostex or other recommended shampoo

[Pragmatar is a very useful combination of sulfur, salicylic acid, and tar, which can be used in place of above prescription]

℞

Selenium sulfide (Selsun) suspension

S Apply once or twice weekly for first two weeks, then less often as required

First wash hair and scalp with the usual shampoo and rinse out Work 1 to 2 teaspoonfuls into scalp until a lather is obtained Rinse out and repeat process Allow Selsun to remain in contact with scalp for at least 5 minutes Rinse out thoroughly

[Beware of toxicity! Should not be used by young children *If hair begins to fall excessively* or becomes increasingly oily, this preparation must be discontinued and replaced by others

or

℞

Sebizon

S Apply to scalp by thorough rubbing in at bed time Brush hair 2 to 3 minutes and allow medication to remain in overnight Repeat for 8 to 10 successive nights If scalp and hair are oily or greasy application should be preceded by a nonirritating shampoo

[In contrast to preceding prescription, this is not likely to cause increased oiliness can be used by young children contains no sulfides and can therefore be used in combination with mercurials as well as sulfur]

or

℞

Sebulex	120

S Massage a liberal amount into the wet hair and scalp for 2 to 5 minutes Rinse and repeat Rinse thoroughly Shampoo in this manner as often as required to keep scalp clean and comfortable

Sulfur-Containing Regimen for Face and Trunk

℞

Pragmatar	
(Cety alcohol coal tar distillate)	4 0
Sulfur precipitate	3 0
Salicylic acid	3 0
O/W Emulsion base ad	100 0

S Apply to affected areas two or more times daily

℞

Resorcinol		1 0 to 5 0
Sulfur precipitate		3 0 to 10 0
Solution of coal tar		3 0 to 10 0
Zinc oxide		
Talci	āā	20 0 to 25 0
Glycerin		10 0
Water		
Alcohol	aa	40 0

S Lotion paint on affected areas 2 or more times daily

℞

Antibiotic lozenges
(*Each troche contains zinc bacitracin 300 U, neomycin sulfate, 5 mg, polymyxin B sulfate, 2,000 U*)

S Place one lozenge in mouth after meals and hold until completely dissolved Average dose *is 3 or 4 lozenges a day*

[Useful in recurrent aphthous stomatitis, bullous eruptions of the mouth, e g, oral pemphigus, ectodermosis erosiva pluriorificialis]

℞

Nuporals
(Dibucaine hydrochloride, 1 0 mg in an inert base)

S Permit 1 lozenge to dissolve slowly in the mouth before eating or drinking, do *not exceed* 8 lozenges in 24 hours

[Useful as local anesthetic for painful mouth lesions as in oral pemphigus and painful forms of stomatitis]

℞

Neomycin solution		0 5%
Neomycin		*250 mg*
Distilled water	ad	50 0

(Must be freshly prepared Keep refrigerated Wide spectrum antibiotic)

S Apply with cotton swab or camel s hair brush 3 or 4 times a day

[Useful in aphthous stomatitis acute herpetic stomatitis Stevens Johnson syndrome, oral pemphigus, Vincent's infection]

℞

Antiseptic solution mouthwash

Boric acid		2 5
Thymol		0 05
Chlorothymol		0 05
Menthol		0 05
Eucalyptol		0 01
Methyl salicylate		0 2
Thyme oil		30 0
Alcohol		30 0
Distilled water	ad	100 0

S Add 2 teaspoonfuls to ½ glassful of warm water Swish through mouth after meals May also be used as a gargle

[Antiseptic, soothing Useful in poor oral hygiene, fetor, bismuth stomatitis, nonspecific forms of stomatitis]

Silver nitrate, as toughened silver nitrate sticks or as 10 per cent aqueou solution can be applied to torpid denuded or ulcerated areas once to twice dail *This should be done only by the physician* and only over short periods becaus of the risk of producing argyria in susceptible individuals

Of course, specific forms of stomatitis, vulvitis, and vaginitis must be treate by specific measures—e g, syphilitic (systemic penicillin), monilial (gentian viole or borax solutions, Mysteclin, etc), gonorrheal (*sulfonamides, antibiotics etc*) vitamin deficiency (appropriate diets and vitamin administrations, etc)

of the antieczematous agents used in acute eczematous dermatitis (page 798) Highly impetiginized forms will often require the milder remedies used as anti-infective agents in impetigos and other pyodermas Moreover, dietary restrictions (low fats and carbohydrates) vitamin adjuvants (especially high doses of thiamine, riboflavine pyridoxine and B_{12}) are considered valuable by many dermatologists

Change of environment exposure to sunlight correction of hormonal and psychic maladjustments may be of some benefit in certain cases

What is more certain is the fact that in chronic and refractory cases, radiation therapy, including the safe small doses of superficial x rays (gonads shielded in persons below 40!) and the effective doses of grenz rays, both as used by qualified dermatologists, are among the most valuable as well as cleanest and safest of measures

Seborrheic dermatitis is a chronic recurrent disease which may require constant management While many cases can be satisfactorily controlled by the above measures, others become refractory and fail to yield, while still others are forerunners of psoriasis

AGENTS USED IN SOAP SENSITIVITY

In some cases of hand eczemas, atopic dermatitis, infantile eczema, generalized dermatitis, generally irritable and/or dry and senile skins alkali hypersensitivity, and other conditions oatmeal colloids (Aveeno) and hydrolyzed cornstarch (Linit, unscented) can be useful to "soften" bath and wash water (See section on Emollients and Demulcents, page 746)

Soap substitutes e g

- Lowila
- pHisoderm
- pHisoHex (contains 3% hexachlorophene)
- Aveeno
- Soyaloid

or

Superfatted soaps and low pH soaps e g

- Basis soap
- Oilatum soap
- Dove soap

It may also be helpful after each washing to oil the skin with such oils as Nivea oil or Lubriderm

AGENTS USED IN STOMATITIS

Many skin diseases are associated with lesions of the mouth and other orificial mucous membranes *Differential diagnoses of skin diseases and their* management therefore require expertness in recognizing and treating various kinds of oral, vulvovaginal, and anal lesions Similarly, recognition and management of lesions of the mucous membranes often require expertness in dermatologic diagnosis and therapy

In the management of different forms of stomatitis the prescriptions which follow are among the useful ones

applying a galvanic electrical current or an electrocoagulating current This can be done only by skilled, trained, and conscientious persons

For the *temporary* removal of hair the many proprietary and cosmetic preparations are based upon their content of sulfides of various kinds and especially today on the thioglycollates These are usually effective and safe for the temporary removal of hair from the axillae, legs, and other portions of the body

ANTIURTICARIAL AGENTS (Agents Used in Urticaria and Urticarial Eruptions)

This section includes acute urticaria, chronic urticaria, and eruptions with pronounced urticarial components such as certain forms of angioneurotic edema multiform erythemas, drug eruptions, and polymorphous light eruptions (See also section on Sun Screens,' page 771) The first and most fundamental step is the search for causal agents and their reduction or elimination In many cases of acute urticaria the causes can be found, but in only a sadly small minority of chronic cases of urticaria or angioneurotic edema will even the most expert and painstaking search discover the causes In all urticarial eruptions the drug treatment consists of palliative measures to be given while the search for causes is going on and as long as the disease continues Acute urticaria and acute multiform erythemas run their course in a matter of days to a few weeks Chronic and recurrent urticaria sometimes lasts for years and can endure for life The essential drugs of choice are

1 Antihistaminics usually given in doses sufficient to suppress the manifestations For this purpose the forms with prolonged and/or delayed action are often the most efficacious (See page 516)

2 Corticosteroids and/or ACTH given in morbidistatic doses, as in pemphigus (see section on Bullous Dermatoses page 732), and lupus erythematosus (see page 753), but in much smaller doses than used initially in these two diseases e g, daily 50 to 150 mg of cortisone acetate or biologically equivalent dose of other corticosteroid The corticosteroids and/or ACTH are to be used only when the situation is serious and has failed to yield to antihistaminics and other remedies It is my observation that some cases respond to ACTH and not to corticosteroids and vice versa some to antihistaminics and not to the hormones, and vice versa I know of no satisfactory explanation for these individual peculiarities in response

The remainder of the drug treatment of urticarias and urticarial eruptions includes

1 Sedatives of the usual types Here one must be particularly on the alert not to give barbiturates, bromides, salicylates, or other drugs to which the patient is hypersensitive and which may be prolonging the eruption or *actually causing it!*

2 Tranquilizers Recently Atarax has been reported effective as a morbidistatic agent in a high percentage of cases of *chronic* urticaria

3 Antipruritics (page 757) Among the older remedies useful on occasion and in emergencies are

℞
Epinephrine hydrochloride solution 1 1 000
S 0 3 to 1 0 ml ' by subcutaneous inject on
(Especially indicated in laryngeal edema!)

SUN PROTECTIVE MEASURES ("Sun Screens")

These are used in cases of photosensitivity, albinism, polymorphous light eruptions, Darier's disease, and in all forms of lupus erythematosus in order to avoid severe sunburn, to promote tanning, to reduce hyperpigmentation, and to protect against chronic actinic damage, keratoses, skin cancer formation, etc. They include physical protection such as all possible avoidance of exposure, exposure only during the early or late hours of the day, shading hats, clothing, heavy covering, and "make-up."

The topical drugs of choice include the following: para-aminobenzoic acid, menthyl anthranilate, tannic acid, and others.

There are numerous "ethical" proprietaries and over the counter preparations and cosmetics containing these ingredients. Examples are Skolex and Almay Sun Protection Lotion.

A simple useful prescription is the following:

℞
Para aminobenzoic acid 4.5
Hydrophilic ointment ad 30.0
S. Apply before exposure to sunlight.

[N.B. This preparation is difficult to compound as the para aminobenzoic acid crystals must be very finely powdered and carefully triturated in the ointment. Moreover this and other preparations containing para-aminobenzoic acid and derivatives are occasionally elicitors of allergic contact dermatitis.]

Systemically, in papular, urticarial, and polymorphous light eruptions, chloroquine phosphate tablets (Aralen tablets), 250 mg., 1 to 3 times daily, will often prevent the eruption if taken 1 to 2 hours before exposure to the sunlight.

℞
A* Fil Cream (contains menthyl anthranilate)

℞
Neo A* Fil Cream (contains Digallol trioleate)

8-Methoxypsoralen (Oxsoralen, methoxsalen), taken by mouth in doses of 20 mg. daily for adults, will in many persons increase the skin's sensitivity to sunlight. However, included in this increased sensitivity is an augmented stimulus to formation of a thicker stratum lucidum and an increase in melanin formation, both of which filter out substantial quantities of the irritating, erythema producing wave lengths of the solar spectrum. Therefore, slowly increasing, carefully graded daily exposures to sunlight while taking methoxsalen by mouth, ½ to 2 hours before the exposures, will in selected subjects lead to protection against sunburn and some degree of increased sun tanning. Nevertheless, the fact that this secondary protection results from a primary increased sensitivity indicates the limitations of the method and the need for delicate adjustment of the early exposures to avoid excessive sunburn.

AGENTS USED FOR THE REMOVAL OF SUPERFLUOUS HAIR (HYPERTRICHOSIS)

There is no safe and effective way of removing hair *permanently* except by destroying the hair root and bottom of the hair follicle by inserting a needle and

THE CHOICE OF DRUGS FOR THE TREATMENT OF POISONING

Alan K Done, M D

INTRODUCTION

Poisoning is a common medical problem which every physician and hospital should be prepared to handle The majority of acute poisonings are either accidental or suicidal, and the emergent circumstances surrounding their occurrence frequently result in confusion and a feeling of helplessness on the part of the one who is in the best position to render lifesaving service to the patient—the physician who is first contacted All too frequently the basic principles of good medical care are forgotten and conservatism is abandoned in favor of ill considered or unnecessarily heroic measures Attempts to identify the poison and to find a specific antidote are often made at the expense of vital supportive measures Few poisons have specific antidotes and the most effective antidote available is of little value to the patient who is not respiring adequately, has circulatory collapse, or is drowning in his own vomitus Moreover, the administration of an antidote tends often to produce a false sense of security Especially might this be true of the administration by lay persons of the so-called 'universal antidote,' which actually is of little value in most instances of poisoning

The approach to the management of poisonings need differ but little from the approach to other medical problems Every effort should be made to identify the poison but indicated symptomatic treatment should not be withheld in the meantime, just as digitalis would not be withheld pending an etiologic diagnosis in the patient with acute congestive heart failure In many instances of poisoning, as in other medical situations, it is both possible and advisable to institute intelligent symptomatic treatment on the basis of a presumptive *clinical* diagnosis *Specific antidotes, when available, should be considered as adjuncts to a general therapeutic program,* much as antibiotics would be looked upon in the treatment of an infection

Occasional poisonings e g, cyanide, represent urgent emergencies wherein specific *measures must be instituted promptly if a fatal outcome is to be avoided* In circumstances such as these it is helpful to have ready access to information regarding the use of antidotes and sources of more detailed discussions than would

℞
Epinephrine in oil injection 1 500
S 0 2 to 1 0 ml deep intramuscularly (buttocks) every 8 to 16 hours as required

SELECTED REFERENCES

Latapi, F, Lavalle, P, Novales, J, and Ortiz, Y Griseofulvin en Micosis Cutaneas

V Mosby Company
Chicago, 1954, The

it of University Hos
York, 1957, Hoeber Harper

Polano, M K Skin Therapeutics, New York, 1952, Elsevier Publishing Co

Sulzberger, Marion B The Pharmacopeia and the Physician The Treatment of Infantile Eczema, J A M A 112 38, 1939

Sulzberger, Marion B, and Baer, Rudolph L Treatment of Pyodermas (Common Pus Forming Infections of the Skin) 1950 Year Book of Dermatology and Syphilology, Chicago,

Sulzberger, Marion
ment ed

Sulzberger, Marion
1953 54

ortisone for

ermatologic

ologic My
Moniliasis
Year Book
Publishers, Inc, p 5

Welsh American Lecture Series, Springfield, Ill,

Witten, the Treatment of Skin Diseases, Ann New

Witten, Acne Vulgaris and Seborrhea Capitis, Pediat

Witten, cne Vulgaris, in Current Therapy, edited by Saunders Co

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The approach to the management of poisonings need differ but little from the approach to other medical problems. Every effort should be made to identify the poison, but indicated symptomatic treatment should not be withheld in the meantime, just as digitalis would not be withheld pending an etiologic diagnosis in the patient with acute congestive heart failure. In many instances of poisoning as in other medical situations it is both possible and advisable to institute intelligent symptomatic treatment on the basis of a presumptive *clinical* diagnosis. Specific antidotes when available should be considered as adjuncts to a general therapeutic program much as antibiotics would be looked upon in the treatment of an infection.

Occasional poisonings, e.g., cyanide, represent urgent emergencies wherein specific measures must be instituted promptly if a fatal outcome is to be avoided. In circumstances such as these it is helpful to have ready access to information regarding the use of antidotes and sources of more detailed discussions than would

be feasible here For this reason poisons for which antidotes are available are listed alphabetically in the section entitled Specific Measures on pages 785, and particularly useful articles on individual types of poisoning are included in the references at the end of the chapter

DIAGNOSIS

In most instances of acute poisoning a history of the accidental or suicidal ingestion of a toxic substance is readily available At times, however, such information may not be given spontaneously It may be intentionally withheld in cases of suicidal or criminal poisoning A patient may not realize that he has been exposed to a potentially toxic substance, and such a history may be forthcoming only after specifically oriented questioning Furthermore, in the case of chronic poisoning exposure may have occurred at some time in the past Children frequently come to the physician with sudden unexplained illnesses which are later found to be due to the accidental ingestion of a toxic substance

Without a history of exposure the diagnosis of poisoning is not likely to be made unless there is a high index of suspicion *The possibility of poisoning should be suspected in any patient with an obscure illness*, particularly when sudden illness strikes a person who was previously well Poisoning should always be considered in the differential diagnosis of unexplained cyanosis, cardiovascular collapse, sudden loss of consciousness convulsions or vomiting There is scarcely a disease which cannot be mimicked by some type of poisoning, especially of the chronic variety The most painstaking inquiry will often fail to uncover a source of poisoning exposure unless questions are directed toward specific possibilities For example, a history that a child habitually chews on painted window sills and furniture is not likely to be provided spontaneously by the parents or to be uncovered in the course of a routine history On the other hand such information would likely be obtained by the physician who considered the possibility of lead poisoning in a child with papilledema convulsions and increased protein content in the spinal fluid Relatively simple chemical tests are available for the identification of certain poisons but definite clues as to likely possibilities must be afforded the chemist if his results are to be available sufficiently early to be of value in the immediate management of the patient

The following have been found to be valuable aids in the accurate diagnosis of the type of poisoning

Obtaining the Container—The poison container and any remaining poison should always be obtained This is important for several reasons (1) it may be of medicolegal importance should a suspicion of criminal poisoning arise (2) the errors which are frequently made by lay persons in reading and interpreting chemical nomenclature will be avoided (3) if the contents are not specified on the label, such information usually can be obtained through a telephone call or telegram to the manufacturer, or from the brand name of the product (see following paragraph) (4) in the case of a prescription the druggist can identify the material from the prescription number, (5) it may be possible to identify the material by its appearance or physical or chemical properties, (6) many manufacturers pro-

vide reliable information relative to treatment of poisoning on the labels of their potentially toxic products, and (7) knowing the amount of material remaining and the amount originally present in the container, it is *possible to determine the maximum* amount which could have been taken

The text by Gleason Gosselin and Hodge lists over 15 000 trade names of products, identifies their constituents, and provides expert information regarding treatment the *Pesticide Handbook* by Frear lists the constituents of a large number of pesticides Rodman enumerates the toxic constituents of different types (cate gories) of household products Wood s article is a valuable reference to the toxic components in plants and the book edited by Buckley and Porges is an excellent treatise on venoms

Searching of the Poisoning Locale—When acute poisoning is suspected, it is often possible to identify the responsible material by conducting a search of the home or other areas in which exposure may have occurred Having a parent return to the home to look carefully about will usually uncover telltale evidence, such as an open bottle and a few spilled tablets In this regard it is important to question older siblings who may have administered medicines or other substances to a very young child The garage, yard, and even the homes, garages, and yards of neighbors should not be neglected if a search of the house does not provide the answer The search is usually facilitated by having some knowledge, based upon clinical impression of what types of materials are likely to have caused the poison ing in question When suicidal poisoning is suspected, the responsible agent may be identified from discarded containers or wrappers found in wastebaskets or gar bage cans Police departments generally are expert and extremely cooperative in uncovering such evidence

It is advisable at times to extend the search for possible sources of poisoning exposure to the patient's place of employment or other activities outside the home For example a number of warehouse workers who suddenly developed unexplained illness were found to have been poisoned with parathion which was leaking from its *shipping container*

Clinical Diagnosis—Many poisonings manifest more or less typical clinical syndromes which if not absolutely diagnostic, at least make it possible to *limit and* pursue further the likely diagnostic possibilities and to institute intelligent sup portive and expectant management For example, hyperpnea stupor, and vomit ing suggest salicylate intoxication, signs of intense parasympathetic stimulation (salivation lacrimation sweating, excessive bronchial and salivary secretions, con striction of pupils etc) in association with weakness and muscle fasciculations suggest organic phosphate insecticide poisoning hyperpyrexia associated with marked dryness of the skin and fixed, dilated pupils suggest poisoning with a belladonna alkaloid Table 54 enumerates clinical signs which may be of value in *the differential diagnosis of* [illegible]
tually any sign or symptom [illegible]
only those which are felt to be [illegible]
are included

The appearance or odor of *the vomitus* or material obtained by gastric lavage may provide additional diagnostic clues Luminescence of the vomitus or urine

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Table 54 *Clinical Signs in the Differential Diagnosis of Some Common Poisonings*

	Vomiting, diarrhea or abdominal pain	*Hematemesis and bloody diarrhea*	*Coma**	*Convulsions*	*Dilated pupils**	*Constricted pupils*	*Respiratory depression*	*Hyperpnea*	*Cyanosis**	*Shock*	*Albuminuria*	Others
Arsenic (acute)	C	C	F	O						C	F	Garlic odor to breath stupor, delirium, muscle spasm
(chronic)	F		O	O							F	Weakness, *coryza symptoms*, skin rashes, liver damage, peripheral neuritis muscle paralysis, and atrophy
Atropine and belladonna alkaloids			O		C			F		O		*Hyperpyrexia, dry skin and mucous membranes* confusion, mania
Barbiturates			C		O	F	C		O	F		*Depressed superficial and deep reflexes*
Carbon monoxide			C	F				C		O	O	Cherry red color to skin and mucous membranes, headache, confusion, intolerant of exertion
Chlorinated hydrocarbons (DDT, chlordane, lindane, etc)	O		F	C								Tremors, confusion
Cyanide			C	F	F		O	C		F		*Odor of bitter almonds on breath or vomitus*
Fluoride	C	C		O						C	F	Tetany if death delayed
Fluoroacetate	F		C	F						F		Pulsus alternans, ectopic beats
Iron salts	C	C								C		
Lead (acute)	C	F	F	F						C	F	*Muscular weakness, pain cramps*
(chronic)	C		C	C	F							Papilledema, confusion, increased spinal fluid pressure and protein anemia, lead lines in long bones (x ray)
Mercury	C	C								F	C	After 1-3 days glossitis, gingivitis, dysentery, renal damage and failure

suggests phosphorus poisoning An intensely pungent, finely granular black powder suggests calcium cyanide, and the diagnosis of cyanide poisoning is further suggested by an odor of bitter almonds to the breath or vomitus A garliclike odor to the breath or vomitus suggests that phosphorus, arsenic, or garlic was ingested Finally, recognizable pills or undissolved capsules may be found

Laboratory Diagnosis —A number of factors sharply limit the clinical value of toxicologic analyses in cases of acute poisoning Techniques for the identification of many intoxicants are available only in specialized laboratories Exceptions are barbiturates and salicylates which can be determined in many clinical laboratories Even when the analyses are readily available, their value is limited by the fact that they are often time consuming and a general toxicologic survey is impossible with the amount of material which could be obtained from a living patient Thus it is essential that careful consideration be given to a differential diagnosis based on clinical signs and the history of possible exposures before specimens are submitted for examination

A simple test which can be performed in any laboratory or physician's office permits the rapid identification of *salicylate* in urine A urine specimen should be boiled briefly in order to volatilize acetoacetic acid, which may give a false positive reaction The addition of a few drops of a 10 per cent ferric chloride solution results in the formation of a blue to violet color in the presence of salicylates The test is of no quantitative value however since a strongly positive test may be found in association with relative low blood levels of salicylate (This test cannot be used to identify aspirin in gastric contents since the color complex is formed only with free salicylic acid) A very simple and highly reliable test applicable to any hospital or clinical laboratory has been devised for measuring salicylate concentrations in blood Because of the frequency with which unknown quantities of salicylates are ingested accidentally by children or with suicidal intent by adults, ready access to salicylate measurements in the blood is extremely valuable The test can be used as an aid in deciding before illness is apparent whether or not hospitalization is advisable for observation or additional treatment

The presence of *methemoglobinemia,* which may be caused by nitrites, chlorates, aniline, acetanilid, and bromates is suggested when blood obtained from the patient is found to be chocolate brown in color and does not become bright red on exposure to air The presence of the abnormal hemoglobin can be confirmed by spectroscopic examination of the blood

REMOVAL OF THE POISON

Perhaps the most valuable single measure in the treatment of acute poisoning is the removal of the poison from the body before it is absorbed Obviously attempts to remove poison lose their effectiveness rapidly with the passage of time and should be made at the earliest possible moment Occasionally, however, it is wise to delay until after institution of other forms of treatment Cyanide exerts its effects so rapidly that death is likely to ensue unless antidotal treatment is begun immediately In strychnine poisoning, fatal convulsions may be precipitated by attempts to empty the stomach unless barbiturate sedation is instituted beforehand

Poisons which have been applied externally should be removed by copious washing with soap and water It is just as important to remove certain poisons, e g, parathion and nicotine, from the skin and mucous membranes as it is to remove them from the stomach, since cutaneous absorption is appreciable

Emesis —Most poisons are in themselves emetics If vomiting does not occur spontaneously, it can often be induced by stroking the posterior pharynx with a finger (with precautions being taken to prevent biting) or other blunt object Emetic drugs are rarely necessary and should be used with caution Emetics act by medullary stimulation either directly or reflexly through irritation of the gastric mucosa With the former type, stimulation occurs first and is followed by depression It is possible, therefore, to increase the severity of symptoms if poisoning is due to a drug which affects the central nervous system Moreover, either type of emetic is likely to be ineffective in the patient who is poisoned with a depressant *Emetics should never be used in a patient who is severely depressed or has ingested a caustic material such as lye* In the severely depressed patient, aspiration of vomitus into the lungs is a grave danger In the patient who has ingested a caustic material, vomiting is likely to result in further damage to an already eroded esophagus

When the employment of an emetic is felt to be justified the most useful drugs are apomorphine and syrup of ipecac Apomorphine is a more certain emetic and can be given parenterally to the patient who will not cooperate by taking an oral preparation The recommended subcutaneous dose is 1 mg for a small child or 6 mg for an adult Syrup of ipecac is somewhat safer and can be given orally in doses of 1 to 4 teaspoonfuls In the home, effective emetics may be prepared by mixing 1 teaspoonful of powdered mustard or 2 teaspoonfuls of salt in a glass of warm water

Gastric Lavage —Gastric lavage if properly performed is a more certain and thorough method of removing poison from the stomach than the production of emesis alone It is *contraindicated in caustic alkali ingestion* where perforation of the stomach or esophagus is a danger and in strychnine poisoning at least until the patient has been sedated sufficiently to prevent the precipitation of convulsions It should be performed very cautiously, if at all in cases of the ingestion of kerosene, furniture polish or other volatile hydrocarbons, in which the consequences of pulmonary aspiration are so dangerous

A number of steps can be taken to enhance the effectiveness of gastric lavage The largest tube which can be passed safely should be used in order to facilitate aspiration of particulate matter and undissolved pills and to prevent frequent plugging of the tube which will delay completion of the procedure Vomiting should be induced prior to lavage if the patient is conscious and has recently eaten or if the poison was in a slowly disintegrating form, such as enteric coated pills Washing of the stomach after initial aspiration of its contents should be accomplished with small volumes of fluid instilled under little pressure Instillation of more than 15 to 20 ml of fluid at a time (or less in small children), or the use of more than very gentle pressure will result in forcing of the remaining poison through the pylorus into the small intestine where it is not recoverable and can be absorbed readily

Methanol	C		C	O	C			C	F	C		Severe acidosis. During recovery: blindness, weakness, impaired renal function
Nicotine	C		O	F	F_1	C	F_2	C		F		Salivation, sweating, mental disturbances
Nitrites, chlorates, acetanilid	F	O	F	O				C	C	F		Methemoglobinemia; chocolate color to skin, mucous membranes, and blood (blood does not turn red on shaking in air); vertigo
Opiates	F		C			C	C		F			Depressed reflexes; improvement with nalorphine or levallorphan
Phosphates, organic	F		F	F		C	F					Intense parasympathetic stimulation; salivation, lacrimation, sweating, excess bronchial and salivary secretions, bronchospasm, hypertension, weakness, muscle fasciculations
Phosphorus	C	C	F	F						F	F	Garlic odor breath and vomitus; luminescence of urine and vomitus. Later: hepatomegaly, jaundice, hemorrhagic diathesis, oliguria, hematuria
Salicylates	vom		F	O†				C		O	O	Urine pos. for acetone and salicylate (ferric chloride test). Respiratory alkalosis → metabolic acidosis†
Strychnine			O	C			F		F	O		Hyperreflexia, opisthotonos, muscle rigidity, apprehension, conscious during convulsions

*Distinct from that associated with shock or exodus
†In children; less frequently or rarely seen in adults
C—Characteristic
F—Frequently seen
O—Occasionally seen
Subscripts 1 and 2—Sequence of occurrence (e.g., hyperpnea followed by respiratory depression)

muscularly in doses of 3 to 6 mg for adults or 0 1 mg per pound of body weight for children every 15 to 30 minutes The above doses are continued until tendon and gag reflexes return or slight facial twitching is observed

Pentylenetetrazol (Metrazol), amphetamine (Benzedrine) and dextro amphetamine (Dexedrine) have also been used with success in severe depression due to barbiturates and other depressants Nalorphine or levallorphan are drugs of choice in the treatment of depression due to morphine and other narcotics (see Narcotics under Specific Measures) Bemegride (Megimide, Mikedimide) is purported to be a structural antagonist to the barbiturates While it is true that this compound can lessen the degree of depression produced by barbiturates or glutethimide there is little evidence that its mode of action differs from or that it is in any way superior to the known analeptics

Convulsions—Convulsions may occur in the course of poisoning with a wide variety of compounds and may be due to a specific excitatory effect of the intoxicant (e g strychnine organic phosphate insecticides chlorinated hydrocarbons) or secondary to such nonspecific phenomena as hypoxia hypocalcemia water intoxication hypoglycemia cerebral edema or systemic metabolic disturbances Measures aimed at correcting these latter factors should be undertaken and may be effective alone in terminating the convulsions Many patients will also require anticonvulsant medications irrespective of the etiology of the convulsions However such medications are likely to be relatively ineffective unless the underlying disturbances are corrected

The use of anticonvulsant drugs is discussed in Chapter 17 The situation with respect to poisoning differs somewhat from the treatment of epilepsy in that drugs which are effective as prophylaxis against convulsions may be ineffective in terminating seizures The cautious use of a barbiturate with rapid onset and short duration of action is the anticonvulsive therapy of choice for chemically induced convulsions If intravenous administration seems indicated the sodium salts of thiopental (Pentothal) pentobarbital (Nembutal), or amobarbital (Amytal) are preferable to phenobarbital sodium since the delayed onset of action of the latter may be cause for overdosage The recommended intravenous dose of amobarbital sodium is 2 5 to 4 mg per pound of body weight in children or 300 to 600 mg in adults *given slowly until the convulsions cease* Intramuscular administration of a barbiturate is safer and should be used in preference to the intravenous route where possible Phenobarbital sodium can be given intramuscularly in doses of 1 5 to 3 mg per pound of body weight in children or 100 to 200 mg in adults Phenobarbital is preferable to other barbiturates for maintenance prophylaxis against subsequent convulsions because of its selective anticonvulsant properties Paraldehyde is a useful adjunct in the treatment of acute central nervous excitation and may be given intramuscularly or rectally in doses of 0 3 ml per pound of body weight in children or 25 to 40 ml in adults If convulsions are protracted and do not respond to the above measures the induction of anesthesia with open drop ether may be advisable For this it is wise to enlist the aid of an experienced anesthetist if possible

Respiratory Problems—Narcosis a frequent cause of respiratory insufficiency in cases of poisoning was discussed previously under Central Nervous Depression

Careful precautions should be taken to prevent aspiration of gastric contents or lavage fluid into the lungs These precautions are particularly important in the patient who is severely depressed or has ingested kerosene furniture polish, or other volatile hydrocarbons The patient should be placed in a head down position either prone or with the head turned to the side An assistant should stand by ready to aspirate the pharynx promptly should vomiting occur When the tube is removed it should be pinched tightly to prevent spillage of its contents into the lungs as the tip passes through the pharynx

Gastric lavage should be continued until the fluid returns clear Antagonists to certain poisons may be used in the lavage fluid or instilled into the stomach after gastric lavage (See individual poisons under Specific Measures)

SUPPORTIVE MEASURES

Supportive measures are at least as important in the treatment of poisoning as the administration of specific antidotes The majority of patients will recover with good supportive care alone and without it the best of antidotes will be of little value Moreover there are few poisons for which there are specific antagonists so that the treatment of most poisonings is entirely supportive With few exceptions the problems which arise are not at all peculiar to poisoning and the approach to management is essentially the same as in the symptomatic treatment of disease The reader is referred to other chapters for more detailed discussions of general supportive measures This section discusses those aspects which are particularly relevant to the treatment of acute chemical poisoning

Central Nervous System Depression (Narcosis)—The use of stimulants to vital medullary centers is discussed in another section (Chapter 11)

There is a widespread tendency to overtreat patients poisoned by depressants. Most of these patients will recover if treated as though they were recovering from anesthesia Support of the circulation maintenance of a patent airway and the use of oxygen and artificial respiration where indicated are imperative

The use and abuse of analeptic drugs has been a subject of much debate Certainly there is no justification for their employment in patients with active reflexes response to pain and adequate respirations Whether analeptics are of value in patients who are more deeply depressed is the point of controversy It has been suggested that better results can be obtained in the treatment of barbiturate poisoning using supportive care alone rather than in combination with analeptics even in patients who are severely depressed It is my opinion that analeptics are rarely indicated but that they are of value if properly used in carefully selected patients These drugs should not be permitted to supplant essential supportive care and their use should be reserved for those patients in whom recovery seems doubtful with supportive care alone No attempt should be made to restore consciousness rather the objective should be to restore and to maintain active reflexes and adequate respiration

Picrotoxin is probably the analeptic of choice for severe barbiturate depression The dose and route of administration depend upon the urgency of the situation Picrotoxin can be given as a continuous intravenous infusion in a dose of 1 mg per minute in adults or proportionately smaller doses in children or intra

Chapter 26 provides a detailed discussion of the use of vasopressor drugs When shock is severe and presumably due to vasodilatation norepinephrine (Levophed) is probably the vasopressor of choice It is given by continuous intravenous infusion the rate of infusion being regulated by the blood pressure response A 4 mg vial of norepinephrine is mixed with a liter of 5 per cent glucose or normal saline Care should be taken that extravasation does not occur, since tissue sloughs may result With less severe degrees of shock phenylephrine (Neo-Synephrine) hydrochloride may be used intramuscularly in a dose of 0 1 mg per kilogram of body weight

The intravenous administration of adrenocortical hormones has been found occasionally to be a valuable adjunct in the treatment of cardiovascular collapse which is refractory to the methods of treatment described previously Hydrocortisone may be given intravenously in a dose of 2 to 4 mg per kilogram of body weight the free alcohol preparation should be diluted in no less than 250 ml of 5 per cent glucose or physiologic saline This preparation has the disadvantage of requiring dilution in and administration of relatively large volumes of fluid in order to achieve the high doses of hormone which are required The succinate or phosphate esters of hydrocortisone can be administered rapidly intravenously in small volumes of fluid The doses are approximately the same as for the free alcohol of hydrocortisone

Acidosis —Metabolic acidosis may occur in the course of poisoning with methyl alcohol phenol polymeric phosphates, formalin and in salicylate intoxication in children The early administration of polyionic solutions containing glucose will often retard the development of severe acidosis If severe metabolic acidosis is present alkali therapy is indicated Either M/6 sodium lactate or 3 75 per cent sodium bicarbonate may be used intravenously as alkalinizing solutions The carbon dioxide of the blood can be used as a rough estimate of the amount of alkali which should be given The amounts of lactate or bicarbonate necessary to elevate the carbon dioxide content of the blood are

	To raise CO_2 content	
	1 mEq /L	1 volume per cent
Sodium bicarbonate	0 058 Gm /Kg	0 026 Gm /Kg
M/6 Sodium lactate	4 2 ml /Kg	1 8 ml /Kg

Only enough alkali should be given to raise the CO_2 content to approximately 15 mEq per liter or 30 volumes per cent

Salicylate Intoxication —Special problems arise with respect to salicylate intoxication in which a mixed acid base disturbance may occur In children metabolic acidosis may be superimposed upon respiratory alkalosis Under these circumstances it cannot be determined on the basis of CO content or combining power whether acidosis or alkalosis is present since these values are reduced in either instance Certain differentiation can be made only with determination of blood pH If acidosis is mild the intravenous administration of a mixture of 1 part of M/6 sodium lactate 1 part of saline and 2 parts of 5 per cent glucose in water is recommended If the status of acid base disturbance cannot be determined but ketosis is present and more than 6 to 8 hours have elapsed following

Failure to establish and maintain an adequate airway will render all other efforts useless This is a particularly difficult problem in the deeply narcotized patient Bronchial and pharyngeal secretions may be copious and should be removed with suctioning The tongue should be prevented from falling back into the pharynx and thus causing obstruction Pulling the mandible forward, extending the neck, and placing the patient in the prone position will usually accomplish this. The use of an oropharyngeal airway and, occasionally, intratracheal intubation may be of value However, these appliances should be removed as soon as the patient arouses sufficiently to 'fight' the airway Tracheotomy may be necessary if more conservative measures fail or the threat of obstruction is expected to persist for more than two or three days Poisoning associated with inhalation of irritating fumes or the aspiration into the trachea of irritating substances may result in laryngospasm and/or laryngeal edema Tracheotomy or intratracheal intubation under such circumstances is lifesaving

Frequent postural changes and the early prophylactic use of antibiotics are important in preventing hypostatic pneumonia in patients with prolonged coma Artificial respiration, including, where necessary the use of a tank respirator, is imperative when respiratory movements become inadequate Although oxygen administration is a valuable adjunct, it cannot replace artificial respiration when spontaneous respirations are ineffective in maintaining adequate gaseous exchange

Oxygen should be used not only in the treatment of respiratory insufficiency but also under any circumstance in which tissue hypoxia occurs, such as shock, carbon monoxide or cyanide poisoning and in the presence of methemoglobinemia In carbon monoxide poisoning, oxygen has a specific action in promoting the dissociation of carboxyhemoglobin Oxygen should be used in poisonings associated with severe central respiratory depression, but one should be prepared to apply artificial respiration, since oxygen administration frequently results in apnea due to removal of the hypoxic stimulus to spontaneous respiration

Pulmonary edema may respond to alcohol vapor inhalation used in conjunction with the usual measures This can be achieved by bubbling oxygen through a 50 per cent solution of ethyl alcohol and administering the mixture by positive pressure

Shock —Shock is a frequent occurrence in acute chemical poisonings and may be the result of a number of factors It may occur because of pooling and extravasation of blood and fluids into the intestinal tract in the course of poisoning with such materials as arsenic, fluoride and phosphorus from a direct vasodepressor effect of the poison or its metabolites (as is thought to be the case in iron poisoning) as a nonspecific effect of tissue hypoxia or metabolic disturbances (poisoning with central depressants, cyanide, fluoroacetate and general protoplasmic poisons), or in association with the trauma and tissue destruction produced by corrosives Thus the treatment of shock due to poisoning should include an attack upon underlying factors as well as replacement of fluids and the administration of vasopressor agents Specific antidotes (if available), oxygen, and intravenous fluids should be given Vasomotor stimulants should be used only for vasomotor collapse and not to support a failing circulation when fluids or blood transfusion is needed to replace diminished blood volume

Acetanilid See Methemoglobinemic poisoning

Acetophenetidin See Methemoglobinemic poisoning

Acetylcholine See Cholinergic compounds

Acids Magnesium oxide magnesium hydroxide (*milk of magnesia*), or *aluminum hydroxide* should be given by mouth at the earliest possible moment to neutralize strong acids and thus prevent or minimize damage to the esophagus and stomach Sodium bicarbonate and magnesium carbonate effectively neutralize acids but they have the disadvantage of releasing carbon dioxide which may cause dangerous gastric distention Demulcents such as milk aluminum hydroxide gel or olive oil should be used after neutralization of the acid

Alkali Attempts should be made to neutralize caustic alkali with a weak acid such as diluted vinegar lemon juice, or orange juice at the earliest possible moment Olive oil should be applied to affected areas and given frequently by mouth if swallowing is possible Theory and experimental and clinical observations suggest that antiphlogistic adrenocortical hormones such as cortisone, hydrocortisone prednisolone, or prednisone may be of benefit in minimizing stricture formation The reader is referred to other sources for discussions of the important problems of esophageal dilatation and the surgical treatment of caustic strictures of the esophagus

Alkaloids Potassium permanganate reportedly destroys many alkaloidal substances including strychnine physostigmine, coniine, and quinine, although there is some question as to its efficiency in this regard It is irritating to the stomach in concentrations of greater than 1 10,000 and care must be taken to ensure that no undissolved particles are present The solution may be used as the lavage fluid

Alphaprodine See Narcotics

Amanita toxins (toxic mushrooms) *Amanita muscaria* produces rapid poisoning with symptoms of intense parasympathetic stimulation (muscarinic effect) Atropinization is the treatment of choice (see Cholinergic compounds) *Amanita phalloides* produces poisoning which is comparatively delayed in onset (6 to 12 hours) and is characterized by damage to cells of the liver, kidney, heart, brain, and other tissues There is no specific treatment for this type of poisoning

Amphetamine The central excitatory effects of amphetamine and related compounds may be reversed dramatically by chlorpromazine (Thorazine) The doses of chlorpromazine which are required are in the upper therapeutic range and are not in themselves depressive This is in contrast to the use of barbiturate, which usually produces a less satisfactory response, and then only in very large doses Moreover, with the small doses of chlorpromazine which are required, postexcitatory depression is not aggravated The suggested dose of chlorpromazine for a 2 year old child is 15 mg intramuscularly

Amyl nitrite See Methemoglobinemic poisoning

Aniline See Methemoglobinemic poisoning

Antimony *See Heavy metals*

Arecoline See Cholinergic compounds

Arsenic See Heavy metals

Barium salts Sodium sulfate forms insoluble salts with barium The recommended dose is 2 to 3 Gm for a 2 to 3 year old child An initial dose is given and then removed by gastric lavage A second dose is given after completion of lavage

Benzedrine See Amphetamine

Bismuth See Heavy metals

Bromide Sodium or ammonium chloride hasten the excretion of bromide The dose and route of administration depend upon how severe *and acute is the* bromide intoxication Mercurial diuretics are also of value in promoting the excretion of bromides

Cadmium See Heavy metals

Caustic soda. See Alkali

Chlorates *See Methemoglobinemic* poisoning

Cholinergic compounds Atropine will reverse the muscarinic effects of cholinergic drugs (e g , acetylcholine pilocarpine methacholine), the toxic mushroom *Amanita muscaria*, and the organic phosphates The muscarinic effects include profuse sweating, excessive secretion

the ingestion of large amounts of salicylate by a small child, the administration of a similar solution would be appropriate With more severe degrees of acidosis, the above mentioned scheme for calculating alkali requirements on the basis of CO_2 content of the blood has been proved highly satisfactory

Oliguria and Anuria.—Acute renal failure may occur in the course of poisoning with a variety of compounds including mercury and other heavy metals, phosphorus, carbon tetrachloride, bromate, and hemolytic substances such as castor beans and naphthalene In most instances renal failure is reversible, and, if the patient is able to survive, kidney function can be expected to resume in from 1 to 3 weeks Consequently the aim of therapy is to prolong the patient's life until function returns Avoidance of overhydration and hyperkalemia are critical problems in management during the period of oliguria or anuria. Fluid intake should be limited to replacement of measurable fluid losses (stool, urine, vomitus) plus insensible water loss Insensible water loss is in the range of 450 to 500 ml per square meter of body surface area at usual room temperatures Balance studies of Bluemle and associates suggest that, at least in adults, a fluid intake of 330 ml per square meter of body surface area, in addition to measured losses, is closer to the true fluid requirement and may be more appropriate for patients with renal failure Additional water loss will occur in the presence of fever, high environmental temperature or hyperventilation under these circumstances daily weights will provide an index as to the adequacy of fluid replacement Estimations of body surface area in children may be obtained from Table 1, page 52 Potassium should be assiduously avoided Protein should be excluded from the diet, and sodium intake should be restricted to replacement of losses

Oral feeding is preferable if it can be accomplished in order that caloric balance may be maintained With resumption of kidney function, diuresis occurs and may be accompanied by dangerous losses of water and electrolytes Careful replacement therapy is then necessary

Since in most instances of renal failure due to poisoning recovery is reasonably certain a conservative approach initially is warranted Hemodialysis (the use of the 'artificial kidney') has been proved to be of value in the treatment of anuria particularly in regard to the control of electrolyte concentrations In the hands of skilled and experienced teams, hemodialysis may be lifesaving, but it is seldom indicated in acute renal failure Peritoneal lavage has been used with success in the treatment of acute renal failure, but has largely been replaced by hemodialysis

SPECIFIC MEASURES (ANTIDOTES)

There are few poisons for which there are specific antidotes The following list includes only those poisons for which chemical antidotes or relatively specific physiologic antagonists are available The discussion of each poison is limited largely to a consideration of the use of the antidotes The reader is referred to the section on Supportive Measures and to the Selected References for a discussion of other aspects of the treatment and the symptomatic treatment of poisoning with compounds for which there are no antidotes

dose of 50 to 100 mg to an adult or 10 to 20 mg to a small child See Chapter 35 for a more detailed discussion of Dicumarol, warfarin, and related compounds

Digitalis Preliminary observations suggest that chelation of serum calcium by the sodium salt of ethylenediaminetetraacetic acid (EDTA, Versene) is effective in the treatment of digitalis intoxication and offers certain advantages over potassium therapy See Chapter 24

Dilaudid See Narcotics

Dromoran See Narcotics

ENP (ethyl *p* nitrophenyl thionobenzene phosphonate) An organic phosphate See Cholinergic compounds

Ferrous sulfate Sodium bicarbonate *(a 5 per cent solution in gastric lavage) will react with* ferrous sulfate to form ferrous carbonate which is less corrosive and less soluble Irritation may be relieved by milk or bismuth subcarbonate Edathamil calcium disodium (Versenate) is capable of chelating iron, and suggestive benefit from its use in the treatment of poisoning with iron salts has been reported (see Heavy metals) Dimercaprol (BAL) increases the mortality in experimental iron poisoning

Fluoride The toxicity of soluble fluoride salts is due in large part to the fact that fluoride is intensely irritating and forms insoluble salts with calcium, the latter effect leading to hypocalcemia The repeated administration of calcium is of value in preventing or correcting hypocalcemia and in binding the fluoride ion Gastric lavage with lime water or the installation of a 5 per cent solution of calcium chloride or large amounts of milk will impede absorption by causing the formation of insoluble calcium fluoride Hypocalcemia should be combated early by the slow intravenous injection of 2 to 10 ml of a 10 per cent solution of calcium gluconate This should be followed *for sustained effect* by the intramuscular injection of similar doses at 4 to 6-hour intervals, with intravenous calcium supplementation as necessary to prevent tetany

Fluoroacetate The toxic effects of fluoroacetate have been attributed to interference with intermediary metabolism Fluroacetate competes with acetate for condensation with oxalacetate fluorocitrate is formed and the tricarboxylic acid cycle is blocked at that point The resulting metabolic derangement manifests itself primarily in disturbances of the central nervous system and the heart, with death resulting usually from ventricular fibrillation

In animal experiments, compounds which are capable of serving as acetate donors have been found to be effective antidotes The most effective and least toxic of the substances studied is glyceryl monoacetate (monacetin) Although therapeutic regimens have not been established in human subjects, studies in monkeys suggest that an appropriate dose would be in the range of 0 1 to 0 5 ml per kilogram intramuscularly at least hourly for several hours Careful monitoring of the cardiac status is essential sufficiently frequent injections of monacetin should be given to prevent or reverse pulsus alternans or electrical alternans on the electrocardiogram Although monacetin has not been evaluated in human subjects, its use seems justified on the basis of its relatively low toxicity and the potentially disastrous results of fluoroacetate poisoning

Formaldehyde Ammonium salts convert formaldehyde to methenamine, which is relatively nontoxic Dilute ammonia water (0 2 per cent) or a dilute solution of ammonium acetate can be used

Glyceryl trinitrate See Methemoglobinemic poisoning

Gold See Heavy metals

Heavy metals Dimercaprol (BAL) is an effective antidote against those heavy metals which form mercaptides with sulfhydryl enzymes It is most effective against arsenic, mercury, and gold and is ineffective against selenium and uranium Other metals occupy an intermediate position Dimercaprol markedly increases the excretion of cadmium but may enhance its nephrotoxicity When dimercaprol therapy is indicated it is important that it be instituted at the earliest possible moment The recommended dose *is 3 to 5 mg per* kilogram of body weight administered intramuscularly every 4 hours for the first 2 days, every 6 hours during the third day and every 12 hours thereafter for 10 days or until recovery is complete Within the 3 to 5 mg per kilogram range, dosage should be dic

of lacrimal, salivary, and bronchial glands, intestinal spasm, tachycardia, bronchospasm and miosis Atropine does not effectively reverse the nicotinic effects (muscle fasciculations and weakness) or effects on the central nervous system (headache, confusion, coma, and convulsions) of these compounds, which must be treated symptomatically It is especially important that artificial respiration be instituted when muscle weakness is sufficiently severe to result in respiratory insufficiency The dose and route of administration of atropine depend upon the severity and urgency of the situation In general, the more intense the symptoms of parasympathetic stimulation the greater the doses of atropine which will be required and the greater the tolerance to atropine

In the case of poisoning with organic phosphate insecticides, atropinization must be rapidly instituted and vigorously pursued because of the grave consequences of inadequate or delayed treatment If symptoms are severe, the initial dose of atropine probably should be no less than 2 mg in the adult and in the range of 0 5 mg in the 2- or 3-year old child It may be advisable to give part of the initial dose intravenously in the severely involved patient Atropine administration should be repeated every 30 to 60 minutes until the desired control is achieved or until signs of atropine overdosage appear Fractional doses should then be given every 4 to 8 hours as necessary to maintain the therapeutic effect

Codeine See Narcotics

Compound 1080. See Fluoroacetate

Cyanide Cyanide combines readily with iron in the ferric state and in this way reversibly inhibits certain cellular oxidizing enzymes such as cytochrome oxidase It does not form a complex with hemoglobin, since such iron is in the ferrous state The most effective method yet devised for the treatment of cyanide poisoning is based upon the intentional conversion of hemoglobin iron from the ferrous to the ferric state (methemoglobin) by the administration of nitrite Methemoglobin completes effectively with cytochrome oxidase for cyanide Sodium thiosulfate is then given to combine with the cyanide, released by the dissociation of cyanomethemoglobin to form thiocyanate, which is excretable and relatively nontoxic

Speed is of the essence, since the course of cyanide poisoning is rapidly fatal Treatment offers some promise of survival even after respiratory arrest has occurred indeed, patients who were thought to be dead have recovered Amyl nitrite should be given by inhalation for 30 seconds of every minute while a sodium nitrite solution is prepared for injection Artificial respiration should be used if the patient is apneic Sodium nitrite is then injected intravenously in a dose of 10 to 15 ml of a 3 per cent solution over a period of 2 to 4 minutes A fall in blood pressure may occur during the injection of nitrite, but this usually will not progress if the rate of injection is slowed momentarily If blood pressure does not return shortly to its previous levels the administration of intravenous fluids or a vasopressor such as ephedrine may be necessary It is advisable to have a slow intravenous infusion operating throughout the course of treatment to provide a ready route for the administration of fluids and vasopressor agents

After injection of sodium nitrite, sodium thiosulfate is injected intravenously through the same needle in a dose of 50 ml of a 25 per cent aqueous solution over a period of 10 minutes If symptoms reappear, the above schedule should be repeated in half doses

Overdosage of nitrite is suggested by deepening cyanosis (due to excessive methemoglobinemia) in the presence of improvement otherwise Oxygen administration will usually suffice to allay symptoms of excessive methemoglobinemia If not, blood transfusion is preferable to inducing a reversion of methomoglobinemia, as would ordinarily be done in the treatment of methemoglobinemia due to nitrite poisoning

Demerol (meperidine) See Narcotics

Demeton An organic phosphate See Cholinergic compounds

Dexedrine· See Amphetamine

DFP (diisopropyl fluorophosphate) An organic phosphate See Cholinergic compounds

Dicumarol The hypoprothrombinemic effects of Dicumarol and warfarin are reversed by vitamin K Vitamin K_1 or K_1 oxide may be given intramuscularly or intravenously in a

biturates and other nonnarcotic central nervous system depressants Nalorphine or levallorphan are so effective and specific in this regard that the diagnosis of poisoning with a narcotic agent should be questioned in a patient who fails to respond Hazardous narcotic withdrawal reactions may be induced by these compounds in addicts

The recommended intravenous dose of nalorphine is 5 to 10 mg in adults and 1 to 2 mg in the small child. Levallorphan doses are approximately one fourth of those of nalorphine In the newborn infant who is depressed from narcotic analgesics given to the mother during labor, levallorphan in a dose of 0 05 to 0 10 mg or nalorphine in a dose of 0 2 to 0 4 mg diluted in 2 to 3 ml of normal saline may be injected into the umbilical vein

One half the initial dose of nalorphine or levallorphan may be given after 10 minutes if adequate spontaneous respiration does not ensue

Neostigmine See Cholinergic compounds

Nickel See Heavy metals

Nicotine If ingested, universal antidote or activated charcoal should be given as a slurry in water, followed by lavage as for Alkaloids Treatment otherwise is strictly symptomatic

Nisentil (alphaprodine) See Narcotics

Nitrites See Methemoglobinemic poisoning

Nitrobenzene See Methemoglobinemic poisoning

OMPA (*octamethyl pyrophosphoramide*) An organic phosphate See Cholinergic compounds

Oxalate Hypocalcemia should be combated as in fluoride poisoning See Fluoride

Pantopon See Narcotics

Parathion An organic phosphate insecticide See Cholinergic compounds

Phenacetin See Methemoglobinemic poisoning

Phenol Olive castor, or other vegetable oils instilled into the stomach will delay the absorption and facilitate removal of phenol

Phosphate organic See Cholinergic compounds

Phosphates polymeric Hexametaphosphate, tripolyphosphate, and pyrophosphate have been shown to produce hypocalcemia and acidosis in rats Personal observations indicate that profound hypocalcemia may occur as well in human subjects poisoned with these compounds Calcium should be administered as in Fluoride poisoning

Phosphorus Gastric lavage with a 0 2 per cent solution of copper sulfate impedes absorption by coating the phosphorus particles with insoluble copper phosphide Treatment otherwise is symptomatic

Pilocarpine See Cholinergic compounds

Potash caustic See Alkali

Potassium bromate See Methemoglobinemic poisoning

Potassium chlorate See Methemoglobinemic poisoning

Potassium hydroxide See Alkali

Prussic acid See Cyanide

Sodium bromate See Methemoglobinemic poisoning

Sodium chlorate See Methemoglobinemic poisoning

Sodium fluoride See Fluoride

Sodium fluoroacetate See Fluoroacetate

Sodium hexametaphosphate See Phosphates polymeric

Sodium hydroxide See Alkali

Sodium nitrite See Methemoglobinemic poisoning

Sodium pyrophosphate See Phosphates, polymeric

Sodium tripolyphosphate See Phosphates, polymeric

Strychnine Fatal convulsions may be precipitated by attempts to empty the stomach unless barbiturate sedation is instituted beforehand Potassium permanganate lavage then should be employed (see Alkaloids) The 'universal antidote can be given as a slurry to delay

tated by the severity of poisoning and the response of the patient Undesirable side effects from dimercaprol itself are rather frequent and include nausea, vomiting, a burning sensation of the lips, mouth, throat and eyes, hypotension, muscle aches, and rarely coma and convulsions Premedication with ephedrine is effective in preventing or minimizing many of these symptoms Dimercaprol appears to be less effective than edathamil calcium disodium in the treatment of lead poisoning and is contraindicated in the treatment of poisoning with iron salts

Edathamil calcium disodium (Calcium Disodium Versenate, EDTA) is an effective chelating agent for those metals (e g, lead and iron) which can be chelated more securely than calcium It appears to be superior to BAL in the treatment of acute or chronic lead poisoning EDTA does not appreciably alter the mortality rate in rats poisoned with iron However, both theory and clinical observations suggest that it deserves more extensive trial in human cases of ferrous sulfate poisoning Only the calcium disodium salt of EDTA should be used in the treatment of poisoning with heavy metals, or dangerous hypocalcemia may result

Edathamil calcium disodium should be administered intravenously in a concentration not exceeding 3 per cent Two infusions a day may be given at a maximum rate per kilogram of body weight of 38 mg per hour or 73 mg per day The course may be continued for 5 to 7 days, the maximum total dose being 550 mg per kilogram An additional course of treatment may be given if necessary, but a rest period of 7 to 10 days between courses is recommended Suggested indications for the second course of therapy include increased concentrations of lead in the blood (greater than 0 1 mg per 100 Gm of whole blood), increase in urinary coproporphyrin excretion (in excess of 250 mcg per 24 hr), or persistence of severe neurologic manifestations

Heroin See Narcotics

H E T P. (hexaethyl tetraphosphate) An organic phosphate See Cholinergic compounds

Hydrocyanic acid See Cyanide

Iodine. A starch solution will neutralize iodine It can be used as the lavage fluid, and the procedure should be continued until the return fluid is no longer blue If starch is unavailable, the immediate swallowing of milk or eggs is of benefit

Iron See Ferrous sulfate

Lye See Alkali

Malathion An organic phosphate insecticide See Cholinergic compounds

Mercury Gastric lavage with sodium formaldehyde sulfoxylate (5 per cent) causes the precipitation of mercury If this is not available, an egg white solution can be used See Heavy metals for specific systemic treatment

Mecholyl See Cholinergic compounds

Meperidine (Demerol) See Narcotics

Methacholine See Cholinergic compounds

Methadone See Narcotics

Methamphetamine. See Amphetamine

Methemoglobinemic poisoning A number of chemicals including nitrite, chlorate and bromate salts, acetophenetidin (phenacetin), acetanilid aniline, and other nitro organic compounds are capable of oxidizing hemoglobin to methemoglobin, which is incapable of transporting oxygen Other effects may be produced as well (e g, the nephrotoxic effects of bromates and chlorates and the hypotensive effects of nitrites), but treatment of manifestations other than methemoglobinemia is symptomatic If methemoglobinemia is severe, it may be reversed by methylene blue Methylene blue can be administered intravenously or intramuscularly in a dose of 1 to 2 mg per kilogram of body weight or orally in a dose of 3 to 5 mg per kilogram The action is much slower by the latter route

Morphine See Narcotics

Mushrooms, toxic. See Amanita toxins

Narcotics. The depressant effects of morphine and its derivatives and the synthetic narcotics are effectively and dramatically antagonized by nalorphine (Nalline) or levallorphan (Lorfan) These compounds do not antagonize the respiratory depression caused by bar-

Partial replacement of blood may be of great benefit in the treatment of poisonings which are associated with the formation of abnormal forms of hemoglobin methemoglobin (poisoning with nitrites, aniline, acetanilid, bromates, chlorates, etc), sulfhemoglobin (poisoning with the same compounds which cause methemoglobinemia), and carboxyhemglobin (carbon monoxide poisoning) The object is to supply normal hemoglobin capable of transporting oxygen This often can be accomplished through simple transfusion However, the amount of blood required may be sufficiently large so that it must be administered by the process of exchange

AN EMERGENCY "KIT" FOR THE TREATMENT OF POISONING

Any hospital, clinic, or individual physician likely to be called upon to provide emergency treatment in cases of poisoning should be prepared by having available at least those drugs which are important in the management of the more common types of poisoning Dangerous delays in the institution of proper treatment can be avoided if these materials are kept together in a poisoning treatment "kit"

Table 55 Suggested Constituents of a Kit for Treatment of Poisoning

Acetic acid 5% (or vinegar)	Methylene blue, 1% aqueous (parenteral)
Activated charcoal	Nalorphine or levallorphan
Ammonia water, 0 2%	Norepinephrine (Levophed) (parenteral)
Amphetamine SO_4 (parenteral)	Olive oil
Amyl nitrite pearls*	Paraldehyde
Amytal sodium (parenteral)	Phenobarbital sodium (parenteral)
Apomorphine (parenteral)	Phenylephrine (Neo Synephrine) HCl (parenteral)
Atropine SO_4 (parenteral)	Picrotoxin (parenteral)
Caffeine and sodium benzoate (parenteral)	Potassium Cl (tablets and parenteral)
Calcium Cl 5% (or lime water)	[illegible]
Calcium gluconate 10% (parenteral)	
Copper SO_4 0 2%	
Dimercaprol (BAL)	
Dithizon†	
Edathamil calcium disodium (EDTA)	
Glyceryl monoacetate (Monacetin)‡	[illegible]
Hydrocortisone succinate or phosphate (parenteral)	Sodium thiosulfate, 25% (parenteral)*
	Starch
Ipecac syrup	Universal antidote
Magnesium hydroxide (milk of magnesia)	Vitamin K or K_1 oxide

*Materials for the antidotal treatment of cyanide poisoning (amyl nitrite, sodium nitrite and sodium thiosulfate) can be obtained ready for use in a kit specifically designed for this purpose from the Eli Lilly Company and includes expert instructions concerning its use

†Preliminary observations suggest usefulness in severe thallium poisoning Availability suggested if thallium is a significant local hazard

‡Experimental evidence of usefulness in fluoroacetate poisoning Availability suggested if fluoroacetate is a significant local hazard

Suggested constituents of such a kit are listed in Table 55 The list does not include intravenous fluids or general supportive drugs which are routinely available in hospitals except for those which are likely to be needed urgently Additional supplies which should be made readily available include equipment for gastric lavage, oropharyngeal airways, a laryngoscope, intratracheal catheters and apparatus for suctioning and for the administration of oxygen

ption pend ng gastric lavage Treatment otherwise is symptomat c and expectant, ting principally of barbiturate sedation and avoidance of sensory stimuli Muscle ants (e g, mephenesin) are reported to be useful adjuncts

An organic phosphate insecticide S e Cholinergic compo inds

hty See Fluoroacetate

(tetraethyl pyrophosphate) An org inic phosphate See Cholinergic compounds

n Potassium chloride and activated charcoal have been shown to increase the ex n of thallium in the urine and feces, respectively Potassium chloride can be ad tered in doses of 3 to 5 Gm per day orally or by vein The recommended dose of ated charcoal is 0 5 Gm per kilogram of body weight twice daily for a period of at 5 days

Dimercaprol (BAL) and edathamil calcium disodium have not been proved effective zon (diphenylthiocarbazone) is capable of chelating thallium and early clinical ience has suggested that this compound may be of considerabl benefit in the treat of severe thallotoxicosis The dose of dithizon is 10 mg per kilogram of body weight daily by mouth or gastric tube It is insoluble in water but may be mixed with gum and suspended in water Further cautious trials of this drug seem warranted

ols See Amanita toxins

n. A Dicumarol like anticoagulant used both medically and as an insecticide See marol

TICIAL REMOVAL OF POISON FROM THE BODY

oisons for which there are no effective antagonists may be absorbed into dy in amounts which, for practical purposes are invariably lethal even with st of supportive care Methods for artificially achieving a reduction in the t of poison in the body offer some hope for recovery under such circum These measures may also be of value when elimination of the poison fails ur, as in renal failure in the case of poisoning with a compound which de upon urinary excretion for removal from the body

emodialysis (The "Artificial Kidney")—The use of hemodialysis in the ent of renal failure has been mentioned under Oliguria and Anuria on page Completely aside from its use in renal failure per se, hemodialysis has been ith some success as a means for rapidly removing large amounts of dialyzable To date, it has been used successfully in the treatment of poisoning with urates, salicylates bromides, thiocyanate and glutethimide Hemodialysis not be expected to remove large molecule poisons which are not dialyzable sons which are irreversibly bound to tissues cells or plasma proteins This lure is not without danger and should be performed only by experienced nel It should be reserved for highly selected instances of very severe ing and should be used in conjunction with careful supportive care

eplacement Transfusion—Replacement (exchange) transfusion has also been sful in achieving a marked reduction in circulating concentrations of a num toxins This procedure offers certain advantages over hemodialysis it is ar to most physicians does not depend upon diffusibility of the toxin requires pecialized equipment and does not require the exceptional experience which essary for the safe use of hemodialysis, especially in the young child It has ovious limitation that, in other than very small children it is technically lt and presents the hazard of transfusion reaction since it may be necessary donor blood from several sources

Lead

Chisolm, J, Jr, and Harrison, H E The Treatment of Acute Lead Encephalopathy in Children, Pediatrics 19 2, 1957

Methemoglobinemia

Bodansky, O Methemoglobinemia and Methemoglob n Producing Compounds, Pharmacol Rev 3 144, 1951

Narcotics

Eckenhoff, J E, Elder, J E, Jr, and King, B D N Allyl Normorphine in the Treatment of Morphine or Demerol Narcosis, Am J M Sc 223 191, 1952

Nicotine

Oberst, B B, and McIntyre, R A Acute Nicotine Poisoning, Pediatrics 11 338, 1953

Phosphates

Gosselin, R E, Tidball, C S, Megirian, R, Maynard, E A, Downs, W L, and Hodge, H C Metabolic Acidosis and Hypocalcemia as Toxic Manifestations of Polymeric Phosphates, J Pharmacol & Exper Therap 108 117, 1953

Phosphorus

Diaz Rivera, R S, Collazo, P J, Pons, E R, and Torregrosa, M V Acute Phosphorus Poisoning in Man A Study of 56 Cases, Medicine 29 269, 1950

Renal Failure

Bluemle, L W, Jr, Potter, H P, and Elkinton, J R Changes in Body Composition in Acute Renal Failure, J Clin Invest 35 1094, 1956

Kolff, W J Acute Renal Failure Causes and Treatment, M Clin North America 39 1, 1955

Swann, R C, and Merrill, J P The Clinical Course of Acute Renal Failure, Medicine 32 215, 1953

Salicylate

Done, A K Salicylate Intoxication, Clin Med 3 755, 1956

Singer, R B The Acid Base Disturbance in Salicylate Intoxication, Medicine 33 1, 1954

Trinder, P Rapid Determination of Salicylate in Biological Fluids Biochem J 57 301, 1954

Winters, R W White, J P, Hughes, M C, and Ordway, N K Disturbances of Acid Base Equilibrium in Salicylate Intoxication, Pediatrics 23 260, 1959

Thallium

Chamberl [illegible] T, and Panos, T C Thallium [illegible]

Lund, A [illegible] on and the Toxicity of Thallium [illegible]

SELECTED REFERENCES

General

Alway R H Acute Po son ng n Ch ldhood n Brennemann s Pract ce of Ped atr cs Hagerstown 1957 W F Pr or Co Inc vol 1 chap 17
Buckley E E and Porges N ed tors Venoms Wash ngton 1956 Amer can Assoc at on for the Ad ancement of Sc ence
Dre sbach R H Handbook of Po sons Los Altos 1955 Lange Med cal Publ cat ons
Frear D E H Pest c de Handbook (Annual Publ cat on) State College Pa College Science Publ shers
[illegible] logy of Commerc al Products
of Therapeut cs ed 2 New
Products J Pediat 46 171

Wood W H Po sonous Plants J Ped at 50 499 1957

Individual Poisons and Problems

Alkali

Carver G M Sealy W C D llon M C Jr Management of Alkali Burns of the Esophagus J A M A 160 1447 1956
F nnerty J J Late Treatment of Caust c Str ctures of the Esophagus S Cl n North Amer ca 34 353 1954
Ray E S and Morgan D L Cort sone Therapy of Lye Burns of the Esophagus J Ped at 49 394 1956

Ba b tu ate

N lsson E On Treatment of Barb turate Po son ng A Mod fied Cl n cal Aspect Acta med scand nav 139 (suppl) 1951

Chol ne g c Compounds

Gordon A S and Frye C W Large Doses of Atrop ne Low Tox ty and Effect veness in Ant chol nesterase Intox cat on J A M A 159 1181 1955
Grob D and Harvey A M The Effects and Treatment of Nerve Gas Po son ng Am J Med 14 52 1953

Cyan de

Chen K K and Rose C L N tr te and Th osulfate in Cyan de Po son ng J A M A 149 113 1952

D g tal s

Gubner R S and Kallman H Treatment of D g tal s Tox c ty by Chelat on of Serum Calc um Am J M Sc 234 136 195

Fluo de

Peters J H Therapy of Acute Fluor de Po son ng Am J M Sc 216 278 1948

Fluo oacetate

Chenoweth M B Kandel A Johnson L B and Bennett D R Factors Influenc ng Fluoroacetate Po son ng Pract cal Treatment W h Glycerol Monoacetate J Pharmacol & Exper Therap 102 31 1951

Heavy Metals

Braun H A Lusky L M and Cal ery H O [illegible] n Therapy of Po son ng by Compounds cury and N ckel J Pharmacol & Exper
Conference Use of Calc um Ethylened am netetra ing A M A Arch Indust Hyg 7 137 1953

I on

Hoppe J O Ma cell G M and Ta nter M L A Rev ew of the Tox c ty of Iron Compounds Am J M Sc 230 558 1955

Lead

Chisolm, J, Jr, and Harrison, H E The Treatment of Acute Lead Encephalopathy in Children, Pediatrics 19 2, 1957

Methemoglobinemia

Bodansky, O Methemoglobinemia and Methemoglobin Producing Compounds, Pharmacol Rev 3 144, 1951

Narcotics

Eckenhoff, J E, Elder, J E, Jr, and King, B D N Allyl Normorphine in the Treatment of Morphine or Demerol Narcosis, Am J M Sc 223 191, 1952

Nicotine

Oberst, B B, and McIntyre, R A Acute Nicotine Poisoning, Pediatrics 11 338, 1953

Phosphates

Gosselin, R E, Tidball, C S, Megirian, R, Maynard, E A, Downs, W L, and Hodge, H C Metabolic Acidosis and Hypocalcemia as Toxic Manifestations of Polymeric Phosphates, J Pharmacol & Exper Therap 108 117, 1953

Phosphorus

Diaz Rivera, R S, Collazo, P J, Pons, E R, and Torregrosa, M V Acute Phosphorus Poisoning in Man A Study of 56 Cases, Medicine 29 269, 1950

Renal Failure

Bluemle, L W, Jr, Potter, H P, and Elkinton, J R Changes in Body Composition in Acute Renal Failure, J Clin Invest 35 1094, 1956

Kolff, W J Acute Renal Failure Causes and Treatment, M Clin North America 39 1, 1955

Swann, R C, and Merrill, J P The Clinical Course of Acute Renal Failure, Medicine 32 215, 1953

Salicylate

Done, A K Salicylate Intoxication, Clin Med 3 755, 1956

Singer, R B The Acid Base Disturbance in Salicylate Intoxication, Medicine 33 1, 1954

Trinder, P Rapid Determination of Salicylate in Biological Fluids, Biochem J 57 301, 1954

Winters, R W White, J P, Hughes, M C, and Ordway, N K Disturbances of Acid Base Equilibrium in Salicylate Intoxication, Pediatrics 23 260, 1959

Thallium

Chamberlain, P H, Stavinoha, W B, Davis, H, Kniker, W T, and Panos, T C Thallium Poisoning, Pediatrics 22 1170, 1958

Lund, A The Effect of Various Substances on the Excretion and the Toxicity of Thallium in the Rat, Acta pharmacol et toxicol 12 260, 1956

Alarming syncope and shock have been reported as sequelae Fatalities have resulted both from immediate reactions of anaphylactic type and from more delayed reactions apparently due to damage of viscera by the injected material There have been similar experiences with the use of other opaque media in the conduct of angiography of the heart and blood vessels Even the new and improved agents for visualization of organs and vessels are not without danger

All of the radioactive substances that serve a purpose in diagnosis are used at present in very small amounts and are not known to exert deleterious effects There is however, increasing suspicion that any radiation of the body is potentially harmful At present, physicians must continue to be anxious lest small amounts of radiation may injure germ plasm the developing embryo, or increase the susceptibility of offspring to leukemia and other diseases

These hazards must be considered separately from recognized contraindications to the diagnostic use of drugs in patients with a history of allergy, known idiosyncrasy, impairment of the function of heart circulation, lungs, liver, or kidney, or chronic debilitating diseases

Danger from diagnostic procedures arises not only from the use of hazardous individual tests but also from the multiplication of relatively simple measures, each of which has its own element of risk Enthusiasm for thorough clinical study may lead to the use of 20 or 30 different diagnostic procedures, some of which are repeated on several occasions

In the practice of modern medicine, discriminating judgment is essential in the selection not only of therapeutic agents but also of diagnostic tests With the wealth of new drugs iatrogenic disease, always frequent, is becoming in the aggregate one of the commonest clinical conditions Not a few of the mishaps and accidents that constitute it have their origin in the well intentioned use of diagnostic measures It behooves all physicians to evaluate thoughtfully the need of every test and to reserve the use of measures involving the introduction of actionable drugs, or possible adverse reactions for those situations where effective management depends upon them

[The sections which follow consider the problems of the choice of drugs as diagnostic agents in the several specialties therefore, only diagnostic tests using drugs are considered Each section was written by the author of the chapter on the choice of drugs for that specialty —Ed]

DIAGNOSTIC TESTS IN HEART DISEASE

WALTER MODELL, M D

preci

coron

tests A special problem in cardiac therapy arises when it is important to know how much digitalis a patient has had prior to examination and circumstances surrounding the case make it impossible to determine this with precision or even to make a reasonable guess Where the exigency of the situation demands a prompt decision, a test which would provide information regarding the state of digitali

THE CHOICE OF A DIAGNOSTIC AGENT

INTRODUCTION

DAVID PRESWICK BARR, M D , LL D , SC D

Diagnostic methods formerly simple have become increasingly complex and frequently involve the use of drugs of which some are ostensibly innocuous while others possess pharmacologic potency or undesirable side actions Modern practice sanctions the use of injections of a variety of organic substances for visualization of the *liver gall bladder urinary tract bronchi lungs, heart, blood vessels* and spinal canal Drugs of variable nature are used in studies of blood flow, blood volume, red blood cell turnover and for diagnosis of diseases such as pernicious anemia amyloidosis or hemochromatosis An increasing number of radioactive substances, including iodine^{131} chromium^{5} and cobalt^{60}, are being introduced as valuable indices of organic function These examples of drugs used in diagnosis are merely indicative The list is not inclusive even for present usage and is constantly being extended

Each test has its own rationale and purpose each may be occasionally or frequently crucial to mature judgment concerning diagnosis, prognosis, or management, and each must be used courageously as clinical situations demand It must be remembered, however, that no one of the occasionally indispensable diagnostic tests may be undertaken without risk

The simplest as well as the most complicated possess inherent dangers Viral or even bacterial infection may be introduced by a needle Sudden death from anaphylactic reaction has followed the intravenous administration of such a relatively inert substance as dehydrocholic acid (Decholin) for the estimation of circulation rate Glucose tolerance tests may be dangerous for patients with Addison's disease because of the severe hypoglycemia that often develops 1 to 4 hours after administration of the sugar Retrograde cystoscopy with opaque organic iodine compounds may be followed by acute renal shutdown The introduction of iodized oil for visualization of the bronchi and upper respiratory tract may produce iodism as well as local obstruction in chronic pulmonary disease

Administration of Diodrast and similar compounds for intravenous urography, although often unaccompanied by serious symptoms is frequently followed by flushing nausea vomiting urticaria venospasm pain in the shoulder or phlebitis

for blood and to indicate by the electrocardiogram the capacity of the coronary circulation to supply more oxygen via the blood, viz, the several standardized exertion tests and the anoxia test

These leave much to be desired, for, on the one hand, they do not produce positive electrocardiographic changes in all instances of coronary artery disease and on the other hand they have been known to precipitate severe anginal attacks and even prolonged attacks of coronary insufficiency Pain is a regular complication

The more recently introduced ergonovine stress test is now being used by some Ergonovine a sympatholytic drug produces no electrocardiographic changes in the normal patient but tends to induce S T segment and T wave changes in patients with coronary artery disease It is by no means definite that this type of stress test is superior to the others, for it is not established that the correlation between disease and positive reactions is appreciably better, while reactions of severe and even prolonged pain also occur after ergonovine in the patient with coronary artery disease One is constrained to speculate whether it is conceivable that any test for coronary artery disease which is based on subjecting a presumably defective coronary circulation to an abnormal stress can be free of the danger of precipitating anginal attacks since stimuli not significantly different are the ones which precipitate the attacks in normal circumstances

Digitalis Tolerance Test —The limitation and the dangers of the test in which the degree of digitalization is determined by the intravenous administration of acetyl strophanthidin are discussed at some length on page 401 The dangers are so substantial that it is difficult to env
least in its present form is defensible
on the interrelationship between bloo
recently been reported Calcium levels in the blood are raised by the administration of calcium salts Further experience is necessary, but the fact that toxic effects can be counteracted instantly by the use of chelating agents makes this a more promising prospect than the acetyl strophanthidin test (see pages 402 and 413)

Drug Sensitivity Tests —

QUINIDINE —The question of quinidine hypersensitivity recurs every time there is, as there now seems to be, a recrudescence of the use of quinidine A preliminary test dose of 0 2 Gm has been suggested as a means of avoiding hypersensitivity reactions While it is conceivable that they may eliminate some serious reactions, such a dose is also large enough to set off full blown reactions in hypersensitive patients There is no good evidence that such a dose, or even a smaller one has been particularly useful in this regard while there have been disasters in patients who responded negatively to the test dose It is probable as has been explained in Chapter 24, that many precipitous reactions are the concomitants of the therapeutic effects of the quinidine and not toxic reactions at all

DIURETICS —Skin tests for sensitivity to diuretics, more especially the mercurial diuretics are not useful Most of the bad results from diuretics have been due to excessive diuresis and the electrolyte disturbances consequent to uncontrolled salt loss Where there is time, explorations of the diuretic effects of small doses are far more likely to lead to optimal dosage than the skin test

zation would be of the utmost use Reactions due to drug sensitivity occur in heart disease much as they do in the therapy of other systems but may seem far more pressing because of the critical status of some patients and the extremely narrow margin for error in heart disease Drug sensitivity tests are therefore also of considerable interest in heart disease

Angiocardiography —The best angiocardiograms are obtained when a large dose of a radiopaque iodide is injected rapidly into the vein It is not surprising therefore that reactions are common The over all death rate has been reported to be around 0 5 per cent that is to say 1 of every 200 patients subjected to this diagnostic procedure may be expected to die Such an accident rate would be considered prohibitive for therapeutic procedures in many serious diseases today even appendectomy has a lower mortality rate

Despite this dismal statistic the risk may be justified The angiocardiogram not only makes the precise diagnosis in some cases but also may provide the surgeon as in coarctation of the aorta with important details for the design of the operation However the angiocardiogram is not always so vital and unfortunately sometimes not useful at all Yet angiocardiography has been applied to cases in which the diagnosis was already established as well as to cases in which it was not conceivable that it could be useful for either surgical or diagnostic purposes Too often neither the limitations nor the dangers of angiocardiography are appreciated by those who order it for their patients it is not in the same class with most other roentgenographic procedures

These considerations become all the more important because of the too often overlooked diagnostic usefulness of cardiac catheterization often where angiocardiography is of little value and sometimes as an alternate diagnostic measure It is surprising to many and not sufficiently well known that despite the fact that catheterization is more complicated and indeed seems far more precarious it is in fact considerably less hazardous than angiocardiography In a series of 6 000 cases a death rate of 0 1 per cent was reported less than one fifth the disaster rate of angiocardiography Thus where either will serve cardiac catheterization is clearly the procedure of choice over angiocardiography the latter is indicated where the former cannot help or fails to help and then only when there is a reasonable expectation that angiocardiography will supply *vital* diagnostic information

Radiopaque Iodides —Several radiopaque iodides are presently available for angiocardiography acetrizoate Urokon) diatrizoate (Hypaque) diatrizoate methylglucamine (Cardiografin) iodomethamate (Neo-Iopax and iodopyracet (Diodrast) While there is no significant difference in catastrophe rate there appears to be an appreciable difference in the rate of minor toxic symptoms after these drugs It is the opinion of some that the desirable highly concentrated solutions of iodine can be injected with fewer reactions in the form of Hypaque than the others and therefore better angiocardiograms can be obtained with Hypaque with a lower incidence of untoward reaction It is to be repeated however that this difference does not apply to the death rate Nevertheless diatrizoate (Hypaque) is presently the drug of choice

Ergonovine Stress Test —Tests to determine the adequacy of the coronary circulation usually involve a scheme to increase the demands of the myocardium

Roth and Kvale, in their original description of the test, indicated that this should exceed the rise caused by the cold pressor stimulus In my experience, any rise in blood pressure of more than 20 mm systolic and 10 mm diastolic above the control reading should be treated as a potential positive reaction It is noteworthy that this usually occurs within 2 to 3 minutes after the injection

If there is no transient blood pressure reduction, a second dose should be given to ensure that (1) the histamine actually enters the vein and (2) an adequate hypotensive stimulus to the adrenals is obtained While it is possible that the stimulus for epinephrine liberation from the adrenal gland is direct and not secondary to an acute fall in blood pressure, this reduction is so common in the average patient as to cast doubt on the validity of the test if it does not occur If the test is suspected of being falsely positive, it may be repeated at a second sitting, if falsely negative, a double dose may be given to exclude definitely the possibility of pheochromocytoma In the event other observations have made the diagnosis strongly probable, the preliminary injection of smaller doses of histamine in order to produce presumably lesser rises in blood pressure is a wise move As little as 0 005 mg of a test dose may produce a marked pressure rise and 0 01 mg may be given subsequently before reaching the full recommended dose If the test with histamine is repeatedly positive or suggestive, the use of tetraethylammonium (TEA, Etamon) 200 mg intravenously, as described by LaDue, while less reliable, is nevertheless a valuable corroborative test

Method of Testing When the Blood Pressure Exceeds 180/110 mm Hg—It is important to remember that many patients with pheochromocytoma may have sustained hypertension or, at least, may have hypertension at the time of the visit to the physician's office To avoid the risk of precipitating a severe hypertensive crisis in these circumstances, it is probably wise to use an adrenolytic drug For this purpose, phentolamine (Regitine), 5 mg intravenously, is preferred No fixed contraindications to such testing exist although the drug may occasionally produce extreme tachycardia and consequently, may induce paroxysms of angina in patients with this disease There is also the possibility of inducing arrhythmias, but this outcome has not been reported

Procedure —The patient should be placed in a quiet room and the blood pressure allowed to reach a base line After the needle has been introduced into the vein and before injection, the blood pressure reading should be repeated to establish that the act of venipuncture has not of itself, artificially elevated the blood pressure After a reasonably stable base line has been achieved and the patient has been appropriately reassured that no symptom except possibly palpitation will follow the test, phentolamine is given intravenously over a 45 second period The blood pressure is then recorded at 30 second intervals for approximately 5 minutes A blood pressure reduction exceeding 25 mm diastolic is considered a positive reaction

Interpretation —It has been my experience that there will be a drop in blood pressure of this magnitude in approximately 10 per cent of hypertensive patients On subsequent testing these patients prove not to have pheochromocytoma The test is not diagnostic because phentolamine has a weak vasodilating and ganglionic blocking activity in addition to being an adrenolytic drug In pa

Circulation Time—A variety of materials have been injected intravenously during the past 30 years to obtain data which, in one way or another, reflect circulation time Some drugs have been used to indicate the time required to produce a detectable odor in expired air after an intravenous injection, presumed to indicate time through the lesser circulation Some drugs have been used in much the same way to produce a detectable taste, presumed to indicate complete circulation time Of a large number only Decholin (sodium dehydrocholate), which produces a bitter taste, continues to be used Reactions to Decholin are by no means rare, some have been serious and a few fatal It is my opinion that the data obtained by means of the intravenous injection of Decholin very rarely provide insights into the state of circulatory dynamics useful for diagnosis or therapy, and the use of Decholin is, therefore, rarely defensible

Sodium succinate has been suggested as a substitute and while it is not yet established that it has any advantage over Decholin in indicating circulation time, it may be that it is superior in that reactions are less common and less severe More experience is needed

THE CHOICE OF DIAGNOSTIC DRUGS FOR THE DISTINCTION BETWEEN PHEOCHROMOCYTOMA AND HYPERTENSION

SIBLEY W. HOOBLER, M.D.

Patients with transient or sustained hypertension are potentially curable if they can be shown to harbor a pheochromocytoma The following diagnostic procedures will usually be satisfactory for making or ruling out the possibility in suspected cases

Patients With Blood Pressures Below 180/110 mm Hg at Time of Testing—For those who have a history of elevated blood pressure, tachycardia, or other presumptive manifestations of pheochromocytoma, the use of histamine intravenously, as suggested by Roth and Kvale, may be effective The following precautions should be taken for this test (1) Patients with angina pectoris or with severe asthma should be tested with great care, if at all (2) The patient should remain in a quiet room and a basal blood pressure reading should be obtained before introduction of the needle He should then be cautioned not to talk, should be guarded against emotional disturbance during the procedure, and should be reassured concerning the expected side effects from histamine injection flushing, headaches, and tachycardia (3) The needle should be left in the vein for 2 to 3 minutes after the injection, and phentolamine (Regitine), 5 mg, should be available for administration in the event of a positive reaction

The dose of 0 05 mg of histamine phosphate, usually diluted to 2 5 ml, is injected intravenously in approximately 15 seconds The blood pressure is determined every 30 seconds for several minutes

INTERPRETATION —The normal response is a brief depression in blood pressure followed by a prompt return to the preinjection levels In the patient with pheochromocytoma, the same events occur except that, following the blood pressure depression, there is a rebound rise of considerable magnitude above the base line

THE CHOICE OF AGENTS FOR GASTROINTESTINAL DIAGNOSIS

THOMAS P. ALMY, M.D., AND HERMAN STEINBERG, M.D.

Introduction —In several of the diagnostic procedures used in gastrointestinal disease, the physician must introduce some chemical compound into the body as a stimulus or a test material Where a choice of these materials is possible, it is important that a maximum of useful information be obtained with a minimum of risk to the patient In this section, consideration will be given to those commonly used laboratory procedures in which the choice of the diagnostic agent is to some degree in the hands of the individual physician, and in which this choice affects not only the usefulness of the test but also the patient s safety or comfort For a fuller discussion of the laboratory methods and the interpretation, reference is made to other publications

Gastric Analysis —In only a few clinical situations is it important to know whether the stomach can secrete hydrochloric acid its absence is helpful in the diagnosis of pernicious anemia and in some circumstances offers presumptive evidence of gastric cancer, its presence contributes to the diagnosis of peptic ulcer and peptic esophagitis, which conversely can be virtually excluded by the demonstration of true achlorhydria On the other hand, because the quantitative variation in output of acid by normal stomachs nearly covers the range of volume and of concentration encountered in disease, and because the ranges of secretory capacity of the stomach in various diseases overlap each other considerably, the quantity of acid secreted even in response to a standard stimulus is rarely of any diagnostic importance

Accordingly, the first and often the only need is to establish the presence or absence of free hydrochloric acid in the stomach If this is present in fasting (basal) secretion recovered by aspiration through a Levin tube, no stimulus is required If the basal specimen is anacid, a number of stimuli may be used, which are listed here in the ascending order of potency

1 *Bread and water*—a slice of bread and 200 ml of water, taken by mouth
2 *Alcohol*—50 ml ethyl alcohol (7 per cent) by stomach tube
3 *Caffeine and Sodium Benzoate*—0 5 Gm orally or subcutaneously
4 *Histamines*

HISTAMINE —Histamine, 0 3 to 0 5 mg (as base) subcutaneously, the most potent of the available stimuli, usually leads to flushing of the skin, sweating, tachycardia, hypotension, and headache At the site of injection a burning sensation appears for a few minutes It is contraindicated in the presence of asthma, angina pectoris, myocardial infarction, and paroxysmal hypertension or other signs of pheochromocytoma

BETAZOLE —Betazole (Histalog) is a synthetic substance closely related to histamine, which is said to be slowly converted to histamine in the tissues and which in doses of 50 mg subcutaneously produces comparable stimulation of the stomach with few of the serious side effects described for histamine

In those patients whose clinical findings indicate the probability of abundant acid secretion, as with a working diagnosis of duodenal ulcer or marginal ulcer, stimulation with caffeine or alcohol is recommended Each specimen should be

tients in whom sympathetic vasomotor tone is prominent in maintaining blood pressure, therefore, blood pressure reduction may occur from excessive sensitivity to sympathetic blockade

The test is useful as a screening maneuver, and, if there is a presumptive positive result, it may be repeated on another occasion or a smaller dose may be tried to attempt to indicate the sensitivity of the patient to the adrenolytic drug If half the usual dose, given over the 45 second interval, produces a significant blood pressure reduction as defined above, the probability of pheochromocytoma is great

False-positive responses have been reported in the presence of hypertension and azotemia and after the use of sedatives and antihypertensive agents such as rauwolfia alkaloids It is, therefore, suggested that all pheochromocytoma testing, particularly with adrenolytic drugs, be performed before therapy is begun In the case of a positive reaction in a patient already under treatment, the treatment should be discontinued before retesting, for 1 or 2 weeks for rauwolfia and for 1 to 2 days for barbiturates and other drugs

Confirmatory Tests —Should the phentolamine response be positive, a test of lesser value is performed with one of the benzodioxanes such as piperoxan (Benodaine), as recommended by Aranow and associates This agent is given by a carefully specified routine over a period of 2 minutes into the vein In patients with essential hypertension, the blood pressure will rise or will show no change

In patients with pheochromocytoma a moderate drop in diastolic blood pressure occurs, usually of lesser magnitude than with phentolamine Should a patient have a positive response the probability of pheochromocytoma is greatly increased It should be emphasized that the benzodioxane test also is sometimes positive in patients who have azotemia or are under the influence of sedatives

In certain cases of severe hypertension, piperoxan may induce a rather sharp pressor rise, and its side effects may, in these cases, resemble those of epinephrine tachycardia, excitation, and a sense of marked anxiety In order to reduce the frequency of these effects, particularly in patients with systolic blood pressures of 250 or more, it is advisable to give the drug slowly in one arm while recording the blood pressure in the other To avoid unpleasant side effects, if there is a sharp rise in blood pressure at the end of the first minute of the injection period the remainder of the drug is not administered and the test is recorded as negative

It should be emphasized that occasionally patients with pheochromocytoma show false negative responses to piperoxan, whereas such a response is very exceptional with phentolamine

Urine Catecholamines —Should the above mentioned tests be suggestive, or some contraindications apply, it is advisable to perform a test for catecholamines in a 24 hour urine sample collected in an acidified specimen bottle This should be done in all suspect cases before exploratory surgery The majority of cases of pheochromocytoma show elevated catecholamine excretion in a 24 hour urine sample, particularly when the blood pressure is elevated, but also frequently even when the blood pressure is normal during the urine collection period

the tips of the tube, placement of one aspirating tip in the stomach and the other in the descending duodenum, continuous aspiration of both lumina, and timed specimens

If these details as well as those of the chemical analytic procedure are meticulously carried out, the procedure can have diagnostic value This value is limited by the fact that the range of normal pancreatic output *is wide and that normal* values can be maintained by only a small group of functional acini properly connected with the duct system and the duodenal lumen Thus, significantly abnormal values can be expected only when a destructive lesion of the pancreas is diffuse (as in pancreatitis), or when a lesion (such as a carcinoma) blocks *both* of the major ducts or, of course, when the gland has been totally removed In patients with chemically proved steatorrhea due to pancreatic deficiency, the measured output of pancreatic juice is nearly always very low Therefore, the finding of a normal output in response to stimulation virtually proves that the steatorrhea is due to an absorptive defect

The *stimuli* commonly used include both hormonal and neurochemical agents reflecting the dual mechanism of natural stimulation of the pancreas

SECRETIN —Secretin is prepared in purified form for intravenous use from *extracts of intestinal mucosa The standard dose is 1 unit per kilogram It is a* protein and as different batches vary in purity to some degree, there is a variable incidence of pyrogenic and allergic reactions The available preparations are essentially free of cholecystokinin The pancreatic juice obtained in this manner is of large volume high in bicarbonate, but poor in enzymes

METHACHOLINE —Methacholine (Mecholyl) is closely related chemically to acetylcholine and, on subcutaneous injection in doses of 10 to 15 mg, reproduces nearly all the effects of strong cholinergic (parasympathetic) stimulation throughout the body The pancreatic juice thus produced is of low volume, poor in bicarbonate but rich in enzymes As cholinergic effects on the heart and bronchi may be dangerous it should never be given to patients *with advanced heart disease,* coronary artery disease, or asthma As it stimulates the glands of the stomach and intestine as well as the pancreas, the resulting duodenal juice is not as good a re*flection of pancreatic secretion* as if secretin were used instead

BETHANECHOL —Bethanechol (Urecholine), 10 mg subcutaneously, may be substituted for methacholine and has somewhat more prolonged effects, making *the timing of the collection of specimens less critical The contraindications* to methacholine apply equally here

Because of greater specificity for the pancreas and better defined standards for the normal response, secretin is the preferred stimulant When it is not available, either of the cholinergic agents may be substituted if *the contraindications are* observed

Excretory Function of the Liver —The presence of jaundice clearly indicates either an absolute or a relative insufficiency *of hepatic excretory* capacity In milder dysfunction of the liver, significant impairment of excretion may be detected by loading" tests and such a test may be the most sensitive and reliable *indication of liver injury*

tested with indicator as it is withdrawn, and the procedure terminated when acid is obtained In the small number who fail to show acid after this stimulus, Histalog or histamine may be given without interrupting the procedure These latter agents should be used at once in those patients in whom the expected result is an achlorhydria (e g, in pernicious anemia) because the absence of acid after other stimuli is not of certain diagnostic value In some elderly patients with vascular disease in whom the diagnosis of pernicious anemia or gastric cancer is suggested by other findings, one is obliged in the interests of their safety to use the milder stimuli first As achlorhydria in pernicious anemia is associated with a deficiency of intrinsic factor measurable by the uptake of Co^{60}-labeled vitamin B_{12} from the intestine (Schilling test), the latter procedure may be substituted As the deficiencies of acid and of intrinsic factor both are permanent and unaffected by therapy, either procedure may be deferred until the patient's condition is improved by specific treatment

While this conservatism in the use of histamine may seem excessive, the occurrence of cardiac and cerebral vascular accidents in elderly individuals and of gastrointestinal hemorrhage in persons with ulcer is frequent enough to make it seem wise

'Tubeless Gastric Analysis —"Tubeless" gastric analysis is the name applied to recently developed techniques for the detection of gastric anacidity by analysis of the urine following the ingestion of ion exchange resins In this procedure azuresin (Diagnex), a carbacrylic resin chemically joined to an azure A radical, is given orally In the presence of gastric hydrochloric acid the azure A is exchanged for hydrogen ion, absorbed from the upper intestine, and promptly excreted in the urine, where its concentration is proportional to the depth of blue or green color In the usual procedure, urine is collected both in the basal state and after gastric stimulation by caffeine and sodium benzoate given orally

There seems no reason to doubt that in the vast majority of instances these 'tubeless" methods provide reliable information as to the presence or absence of acid They are thus preferable to intubation procedures on the basis of acceptance by the patient and saving of the time of technicians and nurses when *surveys* of the population for achlorhydria are undertaken However, in the clinical situations defined above in which the presence or absence of gastric hydrochloric acid enters importantly into the diagnosis, it is better to intubate the patient and detect free acid directly in the gastric juice If none is detected by this procedure, it may be due to improper placement of the tube tip, to admixture with bile or other alkaline juices, to variations in gastric responsiveness, or other factors In such a situation the use of a "tubeless" method provides a valuable check on the validity of the earlier findings

Pancreatic Secretion —While the presence of complete pancreatic achylia can sometimes be established by quantitative tests for trypsin in fasting duodenal juice, the more subtle grades of deficiency of external secretion of the pancreas require quantitative measurement of the output of pancreatic juice in response to a potent stimulus There is no point in doing this *unless care is taken* to ensure quantitative collection of duodenal contents in the manner outlined by Lagerloef, Dreiling, Twiss, and others This involves a double-lumen tube, fluoroscopic visualization of

Iopanoic Acid (Telepaque) The usual dose is 3 to 6 Gm the nigl fore the examination Telepaque gives a very dense shadow in the well fun ing gall bladder It may have the disadvantage of occasionally obs calculi by virtue of the dense shadow it imparts this deficiency, howev more than compensated for by the very excellent outline of the gall bladd dye provides

Iodoalphionic Acid (Priodax) The dosage is the same as for Telepaqu should be given the afternoon prior to the morning of the examination shadow produced by this organic iodide is adequate, but not quite as dense a with Telepaque (iopanoic acid)

INTRAVENOUS CHOLANGIOGRAPHY —When some organic iodides are introc intravenously, the extrahepatic biliary tree may be visualized radiographically w a matter of minutes, thus providing a rapid method of revealing gross pathc changes in the common bile duct The caution to observe prior to the adm tration of an intravenous organic iodide is to test the patient and inquire care into the possibility of an allergic history Side effects such as nausea and h tension are relatively frequent

Intravenous cholangiography is indicated under the following sets of circ stances (1) in patients who continue to have symptoms referable to the bi tract after cholecystectomy, (2) prior to cholecystectomy for calculous di whether or not there has been satisfactory visualization of the gall bladder by cholecystography, and (3) if the patient vomits following the ingestion of the material

Iodipamide (Cholografin) For visualization of the extrahepatic biliary d excluding the gall bladder, the method of choice is the intravenous injectio iodipamide sodium (Cholografin Sodium) or iodipamide methylglucamine (Ch grafin Methylglucamine) (The latter may be preferable because only hal much is injected the doses are the same, however, since the methylglucamine s tion is twice as concentrated as the other) These materials of high iodine con permit visualization of the ducts 15 to 20 minutes after intravenous injection ml of the Cholografin Sodium and 20 ml of the Cholografin Methylglucamı The duct demonstration is far more satisfactory than after the ingestion of l doses of iopanoic acid (Telepaque) and is not inferior to combined oral intr nous cholangiography

Inasmuch as the extrahepatic ducts can be visualized only if the radiopa material is excreted by the liver, severe liver dysfunction, as reflected by ser bilirubin levels above 5 or 6 mg per 100 ml or by Bromsulphalein retent of more than 25 or 30 per cent usually prevents adequate visualization of ducts

Both preparations have given rise to transient side effects such as nausea vom ing and restlessness when injected in less than 10 minutes Sensitivity reactions m be guarded against by careful questioning for a history of allergic manifestatio asthma, urticaria hay fever, and iodine sensitivity The first three are relat contraindications, the last absolute It is recommended that an antihistaminic routinely administered parenterally either immediately before or with the Ch

These tests involve the intravenous injection of a standardized amount of bilirubin or some other substance which depends almost wholly on the liver for excretion The rate of clearance from the plasma becomes a measure of the excretory capacity of the liver if the rate of hepatic blood flow is within normal limits Thus the disappearance of these substances from the plasma will be delayed not only in liver disease but in cardiac failure and shock due to hemorrhage, trauma, myocardial infarction, or the postoperative state False positive results are also obtained in some febrile illnesses and during other pyrogenic reactions The test substances are the following

BILIRUBIN —Bilirubin itself, given intravenously in alkaline solution in doses of 1 mg per kilogram, although in theory the ideal material, in its purified form is expensive and not readily available The variation in normal values obtained is wide Hence it is rarely used in clinical practice

SULFOBROMOPHTHALEIN —Sulfobromophthalein (Bromsulphalein) is a dye which can be readily measured colorimetrically in the plasma It is marketed in standard ampules containing 50 mg per milliliter and is injected intravenously in dosage of 5 mg per kilogram As it is highly irritating to the tissues, it must be given fairly slowly (in approximately 1 minute) and extravasation must be avoided Its purple color is brought out in alkaline medium and hence urine and stools or the returns from a soapsuds enema may turn purple The skin when washed with alkaline soap may take on a reddish purple hue The only significant systemic effect is fever which occurs rarely It can be used in patients with jaundice and may be cleared normally if the jaundice is due to hemolysis or to defective formation of bilirubin glucuronide (constitutional hepatic dysfunction) Otherwise, its use is properly limited to patients with anicteric liver disease or with gastrointestinal hemorrhage

ROSE BENGAL —Rose bengal is so rapidly excreted by the liver that its level in the blood must be measured within a few minutes after injection Unless these specimens can be timed with extreme accuracy serious errors of interpretation may result The photosensitivity of this compound is dangerous For these reasons it is rarely used in clinical practice

The Concentrating Power of the Gall Bladder Oral Cholecystography and Intravenous Cholangiography —

ORAL CHOLECYSTOGRAPHY —Inflammatory and calculous disease of the gall bladder impair the ability of the gall bladder mucosa to absorb and thus to concentrate substances excreted by the liver We take advantage of this deficiency on the part of the diseased gall bladder as a diagnostic test In the presence of adequate liver function, the normally functioning gall bladder will be well outlined by the radiopaque dye on the radiograph The dyes presently in use for cholecystography are administered orally The patient should be asked about iodine sensitivity Mild diarrhea is often encountered and this may be prevented by the oral administration of paregoric with the dye Inasmuch as a greater or lesser (depending upon the substance used) proportion of the dye is excreted by the kidney cholecystography is contraindicated in the patient with acute nephritis or uremia.

100 000 examinations The contraindications to intravenous urography may be listed (1) history of allergy or previous serious reaction to radiopaque iodides (2) blood dyscrasias (particularly hemolytic types), (3) severe electrolyte dis turbances (particularly acid base imbalance), (4) cardiac disease, and (5) hyper pyrexia

TECHNIQUE —It is important to obtain the greatest possible density of the radiopaque material in the collecting system and to dispel adjacent abdominal shadows The patient should not be permitted to take fluids or food for at least 12 hours before the examination To reduce confusing bowel shadows, the pa tient should have a laxative not more than 14 hours prior to examination

If this method of preparation is not possible or is inadvisable, the patient can be prepared by the administeration of 1 ml of Pitressin subcutaneously followed by the intravenous injection of the contrast medium within 30 minutes Pitressin possesses a twofold action on the bowel to expel gas, and on water reabsorption in the renal tubule to concentrate the excreted organic iodide

The patient should be tested for sensitivity by the intravenous injection of a small amount of the dye or by the placing of a drop in the conjunctiva, followed by a wait of 20 minutes for reaction There is some question whether either method of testing sensitivity is entirely dependable, but it is probable that each possesses some merit The specific method of determining sensitivity for the particular product is outlined by the manufacturer in the literature supplied with each ampule

EMERGENCY TREATMENT OF PATIENT REACTIONS —Epinephrine should never be used since it may induce ventricular fibrillation Respiratory stimulants should never be used because they may cause convulsions If cardiac arrest occurs and chest pounding does not re establish cardiac function the chest should be opened within 3 minutes and cardiac massage instituted

Oxygen (100 per cent) should be administered nasally immediately and an *intravenous infusion started* Depending upon the symptoms the following drugs should be given intravenously (1) Seconal, 1 ... han on (2) Benadryl, 20 mg for allergic symptoms ... *for shock or air hunger If not followed by* ... in 1 minute 4 mg of norepinephrine in 500 ml fluid should be ad ... intravenous drip

CONTRAST MEDIA FOR EXCRETORY PYELOGRAPHY —The following are some of the more popular contrast media used in *excretory pyelography* (1) *Diodrast,* (2) Miokon (3) Hypaque (4) Renografin, and (5) Urokon

In my opinion Renografin produces excellent urinary tract shadow In addi tion it is followed by a minimal number of side reactions, making it particularly useful in routine excretory urography

Nephrography —Nephrography, the radiologic demonstration of the renal parenchyma, is p ... not diagnosti cally satisfactory ... *is an ex cellent means of* ... y when it may determine the precise surgical procedure indicated ... yelograms are also desired, the subsequent films are exposed at *the usual intervals for such a study*

THE CHOICE OF DIAGNOSTIC DRUGS IN GYNECOLOGY

M EDWARD DAVIS, M D , AND NICHOLAS W. FUGO, PH D , M D

One of the most important procedures in any sterility study is hysterosalpingography This diagnostic approach will not only determine patency of the fallopian tubes but also visualize the uterine cavity and internal cervical os It will diagnose intrauterine tumors and abnormalities of the tubes such as salpingitis or hydrosalpinx In addition to its value as a diagnostic procedure hysterosalpingography has a definite therapeutic use Not infrequently patients with long histories of infertility will conceive within 3 months after a hysterosalpingogram The explanation for this observation is not definitely known but it is logical to assume that some temporary obstructions are alleviated by this diagnostic aid

Hysterosalpingography when done as part of a sterility workup should be performed during the proliferative stage of the cycle and after all evidence of vaginal bleeding has ceased This timing is to avoid hysterosalpingography when early pregnancy exists

Several agents are available for this purpose Ideally this diagnostic agent has a low viscosity is markedly radiopaque is not irritating to tissues, and is absorbed by the peritoneum slowly, over a period of 6 to 7 days There is no substance which fulfills all of these requirements

One of the most satisfactory of the agents available is purified iodized ethyl ester of poppy seed oil stabilized with 1 per cent poppy seed oil This substance has a high order of radiopacity and has low viscosity as well It is absorbed slowly from the peritoneum if it is confined in a hydrosalpinx it may remain there almost indefinitely

Another preparation which has had increasing use is a mixture of polyvinyl pyrrolidone and sodium acetrizoate This substance is absorbed rapidly from the fallopian tubes and the peritoneum occasionally interfering with a positive demonstration of tubal patency Since its rapid disappearance decreases the likelihood of irritation to tissues hysterosalpingography can be repeated if necessary

THE CHOICE OF DIAGNOSTIC DRUGS FOR UROLOGIC DISORDERS

ROBERT LICH, JR , M D , M S (PATH)

Introduction—Urography is the x ray visualization of the various drainage and reservoir portions of the urinary tract The kidneys and ureters may be visualized by either excretory or retrograde urograms The bladder is demonstrated by cystography and the urethra by urethrography The renal parenchyma is outlined by nephrography and the renal vascular pattern by arteriography

The radiopaque materials used to visualize each of the sections of the urinary tract must produce shadows of adequate density and must have little toxicity as well Nevertheless each involves a risk and to minimize the risk attention must be paid to every detail of procedure The several methods of visualizing the urinary tract by roentgenography will be discussed separately

Excretory or Intravenous Urography.—As benign as this procedure may seem it must be appreciated that one fatal reaction occurs in approximately every

TECHNIQUE —The patient is placed in the recumbent position and the *trast medium is injected into the urethral meatus* In the male, the penis is ge stretched to dispel any folds which might afford a confusing urethrogram film is exposed during the injection of the last 5 ml of the medium

CONTRAST MEDIUM —*Thixokon*, a sterile thickened aqueous solution of toxicity, permits films of excellent contrast

Renal Function Tests —

PHENOLSULFONPHTHALEIN (P S P) TEST —In the average well hydrated tient, the phenolsulfonphthalein is given intravenously This uncomplicated is beyond question a most valuable clinical renal function test and has the at butes of simplicity and safety False P S P values are commonly obtained in presence of residual bladder urine, subcutaneous or intramuscular injection of c dehydration, or circulatory inadequacy

PITRESSIN URINE CONCENTRATION TEST —This test is more rapid, but accurate, than the Mosenthal concentration test It is based upon the effect pituitrin on the tubule cells of the kidney, causing a marked increase in the abso tion of water, followed by a secondary diuresis Epilepsy, angina pectoris, coron thrombosis severe renal failure, toxemia of pregnancy, arteriosclerosis and hyp tension are contraindications

Rational Basis for New Diagnostic Drugs for Urology —The primary co sideration for any new diagnostic drug in urology is the absence of toxic a *allergic reactions In recent years the difficulty of obtaining adequate concentrat* has been overcome The ultimate goal is to provide a drug that can be admir tered orally so that the parenteral route may be avoided and thus materially si *plify the radiographic delineation of the urinary tract*

The methods of determining renal function possess an important deficien in their inability to demonstrate potential renal function Our presently availal *renal function tests provide information only on function at the time of the te* It is true that renal angiography gives some information regarding renal circul tion and thus indirectly, potential renal function may be suggested, but this lac accuracy *Furthermore in order to understand the various clinical manifestatio* of renal pathology more clearly a simple test which would distinguish the functio of the primary units of the kidney is sorely needed

It is obvious from the foregoing that this area of urology is still in its infanc and much is to be accomplished in the future

THE CHOICE OF DIAGNOSTIC AGENTS IN OPHTHALMOLOGY

IRVING H LEOPOLD, M D

Various drugs are used *as diagnostic aids in* ophthalmology Corneal ulcera tion may be determined by simply looking at the eye with the proper typ of light and noting an irregular reflex on the surface This however ca be aided by the instillation of *a drop of sodium fluorescein* Mercurochrome or rose bengal

Mydriatics have been used as a provocative test in angle closure glaucoma

CONTRAINDICATIONS —The contraindications are identical with those of ex- etory urography Nephrography should never be repeated within 24 hours In- dequate veins, in which a 14 gauge needle cannot be used for injection, may pre- nt its use

TECHNIQUE —The precise details are outlined by Wall and Rose

CONTRAST MEDIA —Diodrast Concentrated Solution, Renografin, and Urokon re all used for nephrography, but I think the best results are obtained with 50 ml f 75 per cent Urokon

Renal Arteriography or Aortography —This procedure is hazardous and should e undertaken only by the experienced operator The contrast medium is intro uced rapidly into the abdominal aorta through a needle inserted through the back f an anesthetized patient An immediate postinjection film of the kidneys demon- trates the arterial pattern within the renal substance as well as the contour and aliber of the renal artery This radiographic procedure reveals renal neoplasms, enal cysts, unilateral renal aplasia, renal artery aneurysm, congenital and acquired bnormalities of renal position, and renal vascular inadequacies

CONTRAST MEDIA —Urokon and Renografin are commonly used, but I prefer Neo-Iopax (75 per cent)

Retrograde Urography —This is a means of outlining the collecting system of the kidneys and ureters by injecting the contrast medium into the kidneys hrough ureteral catheters introduced into the renal pelves at the time of cystos copy It is important to inject sufficient dye to fill the renal pelvis and calyces adequately but, at the same time, not to overfill and produce lymphatic or vascu ar reflux The ureters should be completely outlined by injecting as the ureteral catheters are withdrawn Furthermore, in the presence of normal ureteral patency and peristalsis, the kidney and ureter should be free of the contrast medium within 10 minutes of injection

CONTRAST MEDIA —Skiodan and Urokon are commonly used, although any of the intravenous contrast media may be used for retrograde urography, provided the concentration is not greater than 30 per cent I prefer Skiodan (20 per cent)

Cystography —Cystography is useful for outlining the bladder and will reveal the following (1) bladder size, (2) bladder contour, (a) displacement due to extravesical disease or tumor, (b) bladder elevation or "tear drop' deformity due to perivesical hemorrhage commonly associated with fractures of the pelvis, (3) bladder wall irregularities such as rupture of bladder, diverticula cellules of the bladder, tumors of the bladder, (4) nonopaque stones of the bladder, (5) intra vesical projection of the prostate, (6) ureteral reflux

TECHNIQUE —The contrast medium is introduced, by catheter, into the blad- der until the patient complains of vesical distention or until the operator is of the opinion that the amount is adequate

CONTRAST MEDIUM —Sodium iodide (5 per cent) is the most satisfactory, but any organic iodide used in retrograde or excretory urography may be used

Urethrography —This is a study of urethral contour and is useful to reveal the following (1) urethral tumor, (2) stricture, (3) perforation (traumatic, in flammatory), (4) diverticula (5) fistula, and (6) bladder neck pathology (con tracture prostatic hyperplasia)

eenfield, Irving Sodium Succinate as a Test of Circulatory Efficiency, Ann Int Med 44 524, 1950
›wn, B, and Crocker, A T, and Levine, S A Digitalis Tolerance Test, Proc New Eng
A New Quantitative Digitalis n and Digitalis, Am J M Sc

ıeochromocytoma and Hypertension

fford, R W, Roth, G H, and Kvale, W I Evaluation of a New Adrenolytic Drug (Regitine) as a Test for Pheochromocytoma, J A M A 149 1628, 1952
vale, W F, Roth, G M, Manger, W M, and Priestley, J T Pheochromocytoma, Circulation 14 622, 1956
ıDue, J S, Murison, P J, and Pock, G T The Use of Tetraethylammonium Bromide as a Diagnostic Test for Pheochromocytoma, Ann Int Med 29 914, 1948
›th, G M, and Kvale, W F A Tentative Test for Pheochromocytoma, Am J M Sc 210 653, 1945

astrointestinal Disease

am, T H, editor A Syllabus of Laboratory Examinations in Clinical Diagnosis, Cambridge, 1953, The Harvard University Press, pp 310 317 (gastric analysis), pp 333 335 (Bromsulfalein test)
ırsner, J B, Levin, Erwin, Palmer, Walter L, and Ford, Harold Gastric Secretory Response to 3 Beta Aminoethyl Pyrazole in Man, Gastroenterology 20 138, 1952 (On Betazole)
ttman, A, Fox, B W, Kammerling, Erwin M, and Fox, N I A Single Aspiration Caffeine Gastric Analysis in Duodenal Ulcer and Control Patients, Gastroenterology 28 953, 1955
cClenahan, J L, Evans, J A, and Braunstein, P W Intravenous Cholangiography in
gal, H hydria by Tubeless
gal, H With an Azure A
wiss, J Philadelphia, 1955, Lea & Febiger, pp 430 441

rologic Disorders

ntino, W, Zeitel B E, Jacobson, H G, and Poppel, M H Intravenously Given Urographic Mediums, J A M A 161 606, 1956
ch, R, Jr A Compendium of Urology, St Louis, 1954, John S Swift Co, Inc
ch, R, Jr, and Lewis, P J The Use of the Antidiuretic Property of Pitressin in Ex
ndergr C, and Burdick, E D Further lae Following Administration of states, Acta radiol (Supp) 116 84, 1954
all, B, and Rose, D K The Clinical Intravenous Nephrogram, J Urol 66 305, 1951

phthalmology

ınphy, E B, Dowling, J L, and Scott, A Experiences With Radioactive Phosphorus in Tumor Detection, A M A Arch Ophth 57 485, 1957
ıeodore, F H, and Feinstein, R R Practical Suggestions for Preparation and Maintenance of Ste
ıomas, C I, Krohn Localization
ıughn, D A, Jr

tency of the nasolacrimal apparatus can be determined by instillation of a drop containing saccharine or fluorescein

Uveitis that responds to the use of Daraprim rapidly and in a shorter period of time than one would anticipate for a nonspecific response might be indicative of a toxoplasmic etiology A rapid response to tuberculostatic drugs might indicate tuberculous etiology Keratoconjunctivitis sicca may show much staining of the conjunctiva as well as the cornea following the instillation of rose bengal or fluorescein

Sodium fluorescein is usually employed as a 2 per cent solution in distilled water It will reveal any break in the epithelial surface of the cornea or the conjunctiva This solution can become contaminated easily and has been the source of infections of the cornea with *Bacillus pyocyaneus* and other organisms It has been recommended that filter paper be impregnated with fluorescein with a 2 per cent solution and autoclaved Bits of the filter paper are then placed by sterile forceps into the cul de sac and flushed out with normal saline

Provocative Tests for Glaucoma —The intraocular pressure is measured and a drop of 1 per cent Paredrine or 10 per cent Neo-Synephrine is instilled into the cul de sac This may be repeated if wide dilatation is not obtained within 15 or 20 minutes If there has been a rise of 8 mm Hg or more of intraocular pressure following instillation one may consider this a positive provocative test for angle closure glaucoma After completion of the test the pupils should be constricted with 2 per cent pilocarpine nitrate or stronger miotics The provocative dilatation test should be done only after a dark room dilatation test has failed A negative provocative test does not insure that the patient is free of the possibility of angle closure glaucoma

Tolazoline (Priscoline) and vasculat cause a slight rise in intraocular pressure when injected subconjunctivally Since the rise is greater in glaucomatous than in normal eyes it provides a provocative test for early glaucoma Other agents that may be used for provocative tests include 2 per cent cocaine and 2 per cent eucatropine

Radioactive Isotopes —Radioactive P^{32} has been used as an aid in the differential diagnosis of intraocular malignancy Five hundred microcuries of P^{32} are injected intravenously and readings are taken at 1 24 and 48 hours later A positive reading is one which produces a level of at least 30 per cent higher reading over the involved site as compared to a similar area in the opposite eye or an average reading of 30 per cent higher in the involved area as compared to the average of the four quadrants of the opposite eye This test is a diagnostic aid of considerable accuracy The results are to be evaluated along with clinical evidence however and judgment as to the handling of the patient should not be based solely on its results

SELECTED REFERENCES

Heart Disease

Dotter C T and Steinberg I Angiocardiography Baltimore 1952 Williams & Wilkins Co
Gilbert Robert and Lyons Richard H Clinical Evaluation of a Digitalis Tolerance Test Am J M Sc 232 144 1956

ACETYLPHENYLHYDRAZINE
Administration Oral
Dosage form Capsule, 100 mg

ACETYLPROMAZINE
Not available on the commercial drug market

ACETYLSALICYLIC ACID
Synonyms Acetilum, Acetophen, Acetylsal, Aspirin, Aspro, Salacetin, and many others
Trade names Asteric (Brewer), Ecotrin (Smith, Kline & French)
Administration Oral
Dosage form Tablets, 0.1 and 0.3 Gm

ACETYL STROPHANTHIDIN
Not available on the commercial drug market

- **ACETYL SULFISOXAZOLE**
Trade names Gantrisin Acetyl (Roche), Lipogantrisin (Roche)
Administration Oral
Dosage form Solution, 100 mg per kg

ACHROMYCIN (Lederle)
Trade name for Tetracycline

ACHROMYCIN HCl (Lederle)
Trade name for Tetracycline HCl

ACHROMYCIN V (Lederle)
Trade name for Tetracycline PO_4 Buffered

ACHROSTATIN V (Lederle)
Trade name for mixture of Tetracycline PO_4 Buffered and Nystatin

ACID MANTLE CREME (Dome)
Protective cream

ACID MANTLE LOTION (Dome)
Protective lotion

ACIDOLATE (White)
Detergent cleanser

ACIDORIDE (Abbott)
Trade name for Glutamic Acid HCl

ACIDOTHYN (Flint, Eaton)
Trade name for Glutamic Acid HCl

ACIDULIN (Lilly)
Trade name for Glutamic Acid HCl

ACI JEL (Ortho)
Trade name for Ricinoleic Acid

ACLOR (Cole)
Trade name for Glutamic Acid HCl

ACON (Endo)
Trade name for Vitamin A, Water Miscible

ACORTO (Breon)
Trade name for Corticotropin

ACRIFLAVINE BASE
Administration Topical
Dosage forms Tablets, 32 mg , powder

ACRIFLAVINE HCl
Administration Topical
Dosage forms As such, tablets 30, 100 mg troche, 6 mg , ointment 1%

ACTAMER (Monsanto)
Trade name for Bithionol

ACTASE (Ortho)
Trade name for Fibrolysin, Human

ACTH
Synonym for Corticotropin

ACTHAR (Armour)
Trade name for Corticotropin

ACTHAR GEL (Armour)
Trade name for Corticotropin Gel

ACTIDIL (Burroughs Wellcome)
Trade name for Triprolidine HCl

ACTROPE (United)
Trade name for Corticotropin

ACYLANID (Sandoz)
Trade name for Acetyldigitoxin

ADALIN (Winthrop)
Trade name for Carbromal

ADANON HCl (Winthrop)
Trade name for Methadone HCl

ADEMOL (Squibb)
Trade name for Flumethiazide

ADENOSINE MONOPHOSPHATE
Trade name My B Den (Bischoff)
Administration Oral, intramuscular
Dosage forms Tablet, 20 mg , ampule, 100 mg per ml

ADIPHENINE HCl
Trade name Trasentine (Ciba)
Administration Oral intramuscular
Dosage forms Tablet, 75 mg , ampule, 33 mg per ml

DRUG INDEX

ABASIN (*Winthrop*)
Trade name for Acetylcarbromal

ABBOCILLIN (Abbott)
Trade name for Procaine Penicillin

ABMINTHIC (*Pfizer*)
Trade name for Dithiazanine I

ACACIA
Administration Oral
Dosage forms As such mucilage, syrup

ACENOCOUMAROL
Trade name Sintrom (Geigy)
Administration Oral
Dosage form Tablet, 4 mg

ACETAMINOPHEN

mg per ml

ACETANILID
Administration Oral
Dosage form Tablet, 0 2 Gm

ACETAZOLAMIDE
Trade name Diamox (Lederle)
Administration Oral, Intravenous
Dosage forms Tablet, 0 25 Gm scored, vial, 0 5 Gm

ACET DIA MER-SULFONAMIDES
Synonyms *Sulfacetamide Sulfadiazine Sulfamerazine Mixture*
Trade names Cetazine (Bowman), Dorsulfas (Smith Dorsey), Tertiasul (Rorer), Tricombisul (Schering), Trizil (Central)
Administration Oral
Dosage forms Tablets, 0 25 and 0 5 Gm, *solutions of various strengths*

ACETIC ACID
Administration External and by lavage
Dosage form 36% and diluted (6%)

ACETOMEROCTOL
Trade name Merbak (Schieffelin)
Administration Topical
Dosage form Tincture, 0 1%

ACETOPHENETIDIN
Synonym Phenacetin
Administration Oral
Dosage form Tablets, 0 2 and 0 3 Gm

ACETOSULFONE
Trade name Promacetin (Parke, Davis)
Administration Oral
Dosage form Tablet, 0 5 Gm

ACETPYROGALL
Synonym Triacetyl Pyrogallol
Trade name Lenigallol (Bilhuber Knoll)
Administration Topical
Dosage form Ointment 6%

n ACETYL-p-AMINOPHENOL
Synonym for Acetaminophen

ACETYLBROMDIETHYLACETYLCARBAMID
Trade name Sedamyl (Schenley)
Administration Oral
Dosage form Tablet, 0 25 Gm

ACETYLCARBROMAL
Trade names Abasin (Winthrop), Carbased (Mallard)
Administration Oral
Dosage form Tablet, 0 3 Gm

ACETYLDIGITOXIN
Trade name Acylanid (Sandoz)
Administration Oral
Dosage form Tablets, 0 1 and 0 2 mg

ALMINATE (Bristol)
Trade name for Dihydroxy Aluminum Aminoacetate

ALMORA (Durst)
Trade name for Magnesium Gluconate

ALOE
Administration Oral
Dosage form Pill 0 25 Gm

ALOIN
Administration Oral
Dosage form Pill 15 mg

..
Trade name Caytine (Lakeside)
Administration Oral, inhalation, parenteral
Dosage forms Tablet, 2 mg solution 1%, vial 0 5 mg per ml

ALPHAESTRADIOL TRIACETATE
Trade name Estrate (Lakeside)
Administration Intramuscular
Dosage form Ampule 1 mg per ml

ALPHA LACTOSE
Administration Intravaginal
Dosage forms Powder, tablet and capsule, usually made up on prescription

ALPHA LOBELINE HCl
Trade names Lobelin (Bischoff), Lobeline (Sandoz)
Administration Intravenous, intramuscular
Dosage form Ampules 3 and 10 mg

ALPHAPRODINE HCl
Trade name Nisentil HCl (Roche)
Administration Subcutaneous, intravenous
Dosage form Ampules 40 and 60 mg per ml

ALPHA TOCOPHEROL ACETATE
Administration Oral, intramuscular
Dosage forms Capsules, 50 and 100 I U ampule 1 Gm bottle 5 Gm , vial, 200 mg per ml

ALSEROXYLON
Trade names Koglucoid (Panray), Rau Tab (National), Rautensin (Smith Dorsey), Rauwiloid (Riker)
Administration Oral
Dosage form Tablet, 2 mg

ALTAFUR (Eaton)
Trade name for Furaltadone

ALTHOSE (Wyeth)
Trade name for *Methadone HCl*

AL-U CREME (Macallister)
Trade name for Aluminum Hydroxide Gel

ALUDRINE HCl (Lilly)
Trade name for Isoproterenol HCl

ALUDROX (Wyeth)
Trade name for Magnesium and Aluminum Hydroxide Mixture

ALUM
Administration Topical
Dosage form Solution, 1 to 5%

ALUMINUM ACETATE SOLUTION
Synonym Burow s Solution
Trade name Buro-Sol (Doak), Domeboro (Dome)
Administration Topical
Dosage form Solution, 5%

ALUMINUM CARBONATE GEL, BASIC
Trade name Basaljel (Wyeth)
Administration Oral
Dosage form Suspension 50 mg per ml

ALUMINUM Cl
Administration Topical
Dosage form Solution, 25%

ALUMINUM HYDROXIDE GEL
Trade names Alkagel (Lanteen), Al U Creme (Macallister), Creamalin (Winthrop), Vanogel (VanPelt and Brown), Amphojel (Wyeth)
Administration Oral
Dosage forms *Tablet 0 5 Gm , suspensions* of various concentrations

ALUMINUM PENICILLIN
Administration Oral
Dosage form Tablet 50,000 units

ALUMINUM PHOSPHATE GEL
Trade name Phosphaljel (Wyeth)
Administration Oral
Dosage form Suspension, 40 mg per ml

ALURATE (Roche)
Trade name for Aprobarbital

ALZINOX (Patch)
Trade name for Dihydroxy Aluminum Aminoacetate

AMASEC (Lilly)
Each capsule contains Aminophylline, *0 13* Gm Ephedrine HCl, 25 mg , Amobarbital 25 mg

AMBENONIUM Cl
Trade name Mytelase Cl (Winthrop)
Administration Oral
Dosage form Tablets, 10 and 25 mg

ADRENAL CORTEX EXTRACT
Trade name Eschatin (Parke Davis)
Administration Intramuscular, subcutaneous, intravenous
Dosage form Ampule 50 dog units per ml

ADRENALIN (Parke, Davis)
Trade name for Epinephrine

ADRENALIN HCl (Parke Davis)
Trade name for *Epinephrine HCl*

ADRENOSEM SALICYLATE (Massengill)
Trade name for Carbazochrome Salicylate

ADRESTAT (Organon)
Trade name for Carbazochrome Salicylate

ADRIN (Merck)
Trade name for Epinephrine HCl

AEROLONE COMPOUND (Lilly)
Each 100 ml contains Cyclopentamine HCl 0 5 Gm Isoproterenol HCl 0 25 Gm Atropine SO_4 0 1 Gm Procaine HCl, 0 2 Gm

AEROSPORIN (Burroughs Wellcome)
Trade name for Polymyxin B SO_4

AFAXIN (Winthrop)
Trade name for Oleovitamin A

A° FIL (Texas Pharmacal)
Menthyl Anthranilate and Titanium Dioxide cream and stick

AGAR
Synonym Agar Agar
Administration Oral
Dosage form As such

ALBAMYCIN SODIUM (Upjohn)
Trade name for Novobiocin Sodium

ALBOLINE (McKesson & Robbins)
Trade name for Petrolatum

ALBUMIN (HUMAN) SALT POOR
Administration Intravenous
Dosage form Ampule, 0 25 Gm per ml

ALBUMIN, NORMAL (HUMAN) SERUM
Trade name Albumisol (Merck)
Administration Intravenous
Dosage form Ampules, 50 and 250 mg per ml

ALBUMISOL (Merck)
Trade name for Albumin, Normal (Human) Serum

ALCOPARA
Synonym for Bephenium Hydroxynaphthoate

ALDARSONE (Abbott)
Trade name for Phenarsone Sulfoxylate

ALDINAMIDE (Lederle)
Trade name for Pyrazinoic Acid Amine

ALEVAIRE (Winthrop)
Trade name for Superinone

ALFLORONE (Merck)
Trade name for Fludrocortisone Acetate

ALIDASE (Searle)
Trade name for Hyaluronidase

ALKAGEL (Lanteen)
Trade name for Aluminum Hydroxide Gel

ALKAVERVIR
Trade name Veriloid (Riker)
Administration Oral
Dosage form Tablets, 1, 2 and 3 mg

ALLOBARBITAL
Trade name Dial (Ciba)
Administration Oral
Dosage form Tablets 30 and 100 mg

ALLYLBARBITAL
Trade name Sandoptal (Sandoz)
Administration Oral
Dosage form Tablet, 0 2 Gm

ALMAY HYPOALLERGENIC SHAMPOO (Almay)
Nonmedicated shampoo

ALMAY JUNIPER TAR (Almay)
Juniper Tar

ALMAY LIQUID CLEANSER (Almay)
Detergent cleanser

ALMAY PINE (Almay)
Pine Oil

ALMAY SUNBURN PREVENTIVE LIQUID (Almay)
Para aminobenzoic acid liquid

ALMAY SUPERFATTED SOAP (Almay)
Superfatted soap

ALMAY TAR SHAMPOO (Almay)
Tar shampoo

ALMEFRIN (Meyer)
Trade name for Phenylephrine HCl

AMITRENE (Normand)
Trade name for Amphetamine SO_4

AMMIVIN (National Drug)
Trade name for Visammin material

AMMONIATED MERCURY
Synonym White precipitate
Dosage form Ointment, 1 to 5%

AMMONIUM CO_3
Administration Oral
Dosage forms Solutions of various concentrations

AMMONIUM Cl
Trade name Amchlor (Brewer)
Administration Oral
Dosage form Tablets, 0 3 and 0 5 Gm (enteric coated)

AMMONIUM NO_3
Administration Oral
Dosage form Tablet, 0 2 Gm

AMNESTROGEN (Squibb)
Trade name for Estrogenic Substances, Conjugated

AMNIOTIN (Squibb)
Trade name for Estrone

AMOBARBITAL
Trade name Amytal (Lilly)
Administration Oral
Dosage forms Tablets, 8, 16, 50, 100 mg , elixir, 4 and 8 mg per ml

AMOBARBITAL SODIUM
Trade name Amytal Sodium (Lilly)
Administration Oral, intramuscular
Dosage forms Capsules, 60 and 200 mg , vials, 0 125, 0 25, 0 5, and 1 0 Gm

AMODIAQUIN HCl
Trade name Camoquin HCl (Parke, Davis)
Administration Oral
Dosage form Tablet, 200 mg

AMOEBICON (C M C)
Trade name for Glycobiarsol

AMOLANONE HCl
Trade name Amethone HCl (Abbott)
Administration Oral, intramuscular, intraurethral
Dosage form Capsule, 50 mg , vial 20 ml (9%) to be diluted to 500 ml (0 33%) before using

AMPHEDRINE (VanPelt & Brown)
Trade name for Amphetamine SO_4

l AMPHETAMINE ALGINATE
Trade name Levonor (Nordmark)
Administration Oral
Dosage form Tablet, 5 mg

AMPHETAMINE PO_4
Trade name Raphetamine PO_4 (Strasenburgh)
Administration Oral, intravenous
Dosage forms Vial, 10 ml containing 20 mg per ml , tablet, 5 mg

AMPHETAMINE RESIN COMPLEX
Trade name Biphetamine Resin (Strasenburgh)
Administration Oral
Dosage form Capsule, 20 mg

AMPHETAMINE SO_4
Trade names Amphedrine (VanPelt & Brown), Benzedrine SO_4 (Smith, Kline & French), Linampheta (Lincoln)
Administration Oral, intravenous
Dosage forms Tablets, 5 mg , 10 mg , ampule, 1 ml containing 20 mg

AMPHEX (Algro)
Trade name for *Dextro Amphetamine SO_4*

AMPHOJEL (Wyeth)
Trade name for Aluminum Hydroxide Gel

AMPHOTERICIN B
Trade name Fungizone (Squibb)
Administration Intravenous
Dosage form Ampule, 2 5 mg per ml

AMPROTROPINE PO_4
Trade name Syntropan (Roche)
Administration Oral
Dosage form Tablets, 50 and 100 mg

A M T (*Wyeth*)
Trade name for Magnesium Trisilicate and Aluminum Hydroxide

AMYLGESTIN (McNeil)
Trade name for Pancreatin

AMYL NITRITE
Administration Inhalation
Dosage form Fabric covered ampules containing 0 3 ml

AMYLSINE HCl (Novocol)
Trade name for Naepaine HCl

AMYTAL (Lilly)
Trade name for Amobarbital

AMYTAL SODIUM (Lilly)
Trade name for Amobarbital Sodium

AMBODRYL HCl (Parke, Davis)
Trade name for Bromodiphenhydramine HCl

AMBUTONIUM Br
Administration Oral
Dosage form Tablet, 10 mg

AMCHLOR (Brewer)
Trade name for Ammonium Cl

AMEND S SOLUTION
Administration Oral
Dosage form Solution, contains 14 mg Iodine per ml

AMETHOCAINE HCl
Synonym for Tetracaine HCl

AMETHONE HCl (Abbott)
Trade name for Amolanone HCl

AMETHOPTERIN
Trade name Methotrexate (Lederle)
Administration Oral
Dosage form Tablet 2 5 mg

d AMFETASUL (Pitman Moore)
Trade name for Dextro Amphetamine SO

AMIDONE HCl
Synonym for Methadone HCl

AMIDOPYRINE
Synonym for Aminopyrine

AMID SAL (Glenwood)
Trade name for Salicylamide

AMINITROZOLE
Trade name Tritheon (Ortho)
Administration Oral
Dosage form Tablet, 100 mg

AMINOACETIC ACID
Synonym Glycine
Administration Oral
Dosage form As such

AMINOACETIC ACID AND CALCIUM CARBONATE
Trade name Titralac (Schenley)
Administration Oral
Dosage forms Tablet, 0 5 Gm , powder as such

AMINOACETIC FERROUS SO COMPLEX
Trade name Ferronord (Nordmark)
Administration Oral
Dosage form Tablet, 40 mg ferrous iron

AMINOCARBOFLUORENE
Trade name Pavatrine (Searle)
Administration Oral
Dosage form Tablet, 125 mg

AMINO METHYL-NAPHTHOL HCl
Trade name Synkamin (Parke, Davis)
Administration Oral parenteral
Dosage forms Capsule, 4 mg , ampule, 1 mg per ml

AMINOPENTAMIDE
Trade name Centrine (Bristol)
Administration Oral
Dosage forms Tablet, 0 5 mg liquid, about 0 75 mg per ml

AMINOPHYLLINE
Synonym Theophylline with Ethylenediamine
Administration Oral, intramuscular, intravenous
Dosage forms Tablets, 0 2, 0 3 Gm [illegible] pules for intravenous injection [illegible] per ml , for intramuscular injection [illegible] per ml

AMINOPTERIN SODIUM [illegible]
Trade name for Sodium [illegible] tamate

AMINOPYRINE
Trade name Pyramidon (Winthrop
Administration Oral
Dosage form Tablets, 0 2 [illegible]

AMINOSALICYLIC ACID
Synonym Para Aminosalicylic [illegible]
Trade names Pamisyl (Parke Davis [illegible] Pas (Gold Leaf), Parasal [illegible] pasa (Merck)
Administration Oral
Dosage forms Tablet, 0.5 Gm [illegible], 0 5 Gm

AMINOTRATE
Trade names Metamine [illegible] tamin (Squibb)
Administration Oral
Dosage form Tablet, 2 mg

AMIPHENAZOLE
Synonym for Daptazole

AMISOMETRADINE
Trade name Rolicton [illegible]
Administration Oral
Dosage form Tablet, 4 [illegible]

AMITHIOZONE
Synonym Contebe[illegible]
Trade names Pa[illegible] (Schenley)
Administration O[illegible]
Dosage form Tab[illegible]

ANTIMONY SODIUM TARTRATE
Not readily available on the commercial drug market

ANTIMONY SODIUM THIOGLYCOLLATE
Administration Intramuscular intravenous
Dosage form Ampule, 5 mg per ml

ANTIMONY THIOGLYCOLLAMIDE
Administration Intramuscular intravenous
Dosage form Ampule, 4 mg per ml

ANTIPYRINE
Synonyms Analgesine, Anodynine, Parodyne, Phenazone, Phenylone, Pyrazoline, and many others
Administration Oral
Dosage form Tablets 0 2 and 0 3 Gm

ANTISTINE (Ciba)
Trade name for Antazoline HCl

ANTRENYL Br
Trade name for Oxyphenonium Br

ANTRYPOL
Synonym for Suramin Sodium

ANTUITRIN (Parke Davis)
Trade name for Chorionic Gonadotropin

ANTURAN (Geigy)
Trade name for Sulfinpyrazone

ANZOL (Veltex)
Trade name for Benzethonium Cl

APAMIDE (Ames)
Trade name for Acetaminophen

APEXOL (Roerig)
Trade name for Oleovitamin A

A P L. (Ayerst)
Trade name for Chorionic Gonadotropin

APOMORPHINE HCl
Administration Subcutaneous
Dosage form Hypo tablet

APRESOLINE (Ciba)
Trade name for Hydralazine HCl

APROBARBITAL
Trade name Alurate (Roche)
Administration Oral
Dosage form Elixir, 7 5 mg per ml

AQUADIOL (National Drug)
Trade name for Estradiol

AQUAPHOR (Duke)
Hydrophilic ointment base

AQUASOL A (U S Vitamin)
Trade name for Vitamin A, Water Miscible

AQUA TESTERONE (Endocrine)
Trade name for Testosterone

AQUATYL (Irwin, Neisler)
Trade name for Dioctyl Sodium Sulfosuccinate

AQUIOL (Estro)
Trade name for Estradiol

ARALEN PO, (Winthrop)
Trade name for Chloroquine PO

ARAMINE BITARTRATE (Merck)
Trade name for Metaraminol Bitartrate

ARANTHOL (Bilhuber Knoll)
Trade name for Methamoctol

ARCOFAC (Armour)
Trade name for Cholesterol Lowering Factor

AR EX TAR (Ar Ex)
Trade name for Juniper Tar

ARFONAD (Roche)
Trade name for Trimethaphan Camphor sulfonate

l ARGININE HCl
Trade name R Gene (Cutter)
Administration Intravenous
Dosage form Solution 5%

ARGYROL (Barnes)
Trade name for Silver Protein, Mild

ARISTOCORT (Lederle)
Trade name for Triamcinolone

ARISTOL (Merck)
Trade name for Thymol I

ARLIDIN HCl (Arlington)
Trade name for Nylidrin HCl

ARMAZIDE (Armour)
Trade name for Isoniazid

ARSENIC TRIOXIDE
Administration Oral
Dosage forms Tablet, 1 0 mg , solution, 1%

ARSTHINOL
Trade name Balarsen (Endo)
Administration Oral
Dosage form Tablet, 100 mg

ANAHIST (Anahist)
Trade name for Thonzylamine HCl

ANALGESINE
Synonym for Antipyrine

ANAYODIN (Bischoff)
Trade name for Chiniofon

ANDIRA (Maney)
Trade name for Pectin

ANDRODIOL (Carnrick)
Trade name for Methandriol

ANDROLIN (Lincoln)
Trade name for Testosterone

ANDROLIN IN OIL (Lincoln)
Trade name for Testosterone Propionate

ANDROLONE (National)
Trade name for Stanolone

ANDROMETH (Central)
Trade name for Methyltestosterone

ANDRONAQ (Central)
Trade name for Testosterone

ANDRONATE (Central)
Trade name for Testosterone Propionate

ANDRUSOL (C D Smith)
Trade name for Testosterone

ANDRUSOL P (C. D Smith)
Trade name for Testosterone Propionate

ANECTINE Cl (Burroughs Wellcome)
Trade name for Succinylcholine Cl

ANESTHESIN (Abbott)
Trade name for Ethyl Aminobenzoate

ANGICAP (Pro Acet)
Trade name for Pentaerythritol Tetranitrate
Sustained release capsules containing three 10 mg doses released separately at timed intervals

ANGITET (Harvey)
Trade name for Pentaerythritol Tetranitrate

ANILERIDINE HCl
Trade name Leritine HCl (Merck)
Administration Oral
Dosage form Tablet 25 mg

ANILERIDINE PO_4
Trade name Leritine PO (Merck)
Administration Parenteral
Dosage forms Ampules 25 mg per ml vial 25 mg per ml

ANISE OIL
Administration Oral
Dosage forms As such spirit

ANISINDIONE
Trade name Miradon (Schering)
Not available on the commercial drug market

ANODYNINE
Synonym for Antipyrine

ANSADOL (Rorer)
Trade name for Salicylanilide

ANSOLYSEN (Wyeth)
Trade name for Pentolinium

ANTABUSE (Ayerst)
Trade name for Disulfiram

ANTAZOLINE HCl
Trade name Antistine (Ciba)
Administration Oral, topical
Dosage Tablet 100 mg solution 0 5%

ANTEPAR CITRATE (Burroughs Wellcome)
Trade name for Piperazine Citrate

ANTHALAZINE (Bowman)
Trade name for Piperazine Hexahydrate

ANTHIOMALINE
Synonym for Lithium Antimony Triomalate

ANTHRALIN (Abbott)
Trade name for Dihydroxyanthranol

ANTIHEMOPHILIC GLOBULIN
Administration Intravenous
Dosage form Ampule 200 mg

ANTIHEMOPHILIC PLASMA (HUMAN)
Administration Intravenous
Dosage form Vial to be diluted to 50 and 100 ml equivalent to 60 and 120 ml of plasma

ANTIHIST (Lipton)
Trade name for Pyrilamine Maleate

ANTIMONY POTASSIUM TARTRATE
Administration Intravenous
Dosage form Ampule, 10 mg per ml

AZOCHLORAMID (Wallace & Tiernan)
Trade name for Chloroazodin

AZODYNE (Stuart)
Trade name for Phenylazo-diamino pyridine HCl

AZULFIDINE (Pharmacia)
Trade name for Salicylazosulfapyridine

AZURESIN
Trade name Diagnex Blue (Squibb)
Administration Oral
Dosage form Powders in set of packets

BACITRACIN
Trade names Parentracin (C S C), Topitracin (C S C)
Administration Topical, intramuscular
Dosage forms Ointment, 500 units per Gm vial, 50,000 units suppository, 10 000 units

BAL
Synonym for Dimercaprol

BALARSEN (Endo)
Trade name for Arsthinol

BANOCIDE
Synonym for Diethylcarbamazine

BANTHINE Br (Searle)
Trade name for Methantheline Br

BARBITAL
Synonyms Veronal Barbitone
Administration Oral
Dosage form Tablet or capsule, 0 3 Gm

BARBITAL SODIUM
Trade name Medinal (Warner Chilcott)
Administration Oral, rectal
Dosage form Tablet, 320 mg

BARBITONE
Synonym for Barbital

BARIUM SO_4
Administration Oral
Dosage form As such

BASALJEL (Wyeth)
Trade name for Aluminum Carbonate Gel, Basic

BASERGIN (Sandoz)
Trade name for Ergonovine Tartrate

BASEX (Columbus)
Trade name for Polyamine Methylene Resin

BASIS SOAP (Duke)
Trade name for Superfatted soap

BEADOX HCl (Premo)
Trade name for Pyridoxine HCl

BELLADONNA
Administration Oral
Dosage form Tincture

BELLADONNA EXTRACTS
Trade names Bellafoline (Sandoz), Vinobel (Merrell)

BELLAFOLINE (Sandoz)
Trade name for Belladonna Extract

BEMEGRIDE
Trade names Megimide (Abbott), Mikedimide (Panray)
Administration Intravenous
Dosage form Ampule, 5 mg per ml

BENACTYZINE HCl
Trade names Phobex (Lloyd), Suavitil (Merck)
Administration Oral
Dosage form Tablet, 1 mg

BENADRYL (Parke, Davis)
Trade name for Diphenhydramine HCl

BENASEPT (Blue Line)
Trade name for Benzalkonium Cl

BENEMID (Merck)
Trade name for Probenecid

BENODAINE HCl (Merck)
Trade name for Piperoxan HCl

BENOQUIN (Elder)
Trade name for Monobenzone

BENOXINATE HCl
Trade name Dorsacaine HCl (Dorsey)
Administration Topical
Dosage form Solution, 0 4%

BENTONITE
Adsorbent, emulsifier, gel former

BENTYL HCl (Merrell)
Trade name for Dicyclomine HCl

BENZALKONIUM Cl
Trade names Benasept (Blue Line), Roccal (Winthrop), Zephiran Cl (Winthrop)
Dosage forms Solutions, 12 8% and 0 1%, tincture, 0 1%

ARTANE HCl (Lederle)
Trade name for Trihexyphenidyl HCl

ARTHENOLONE (Ayerst)
Trade name for Pregnenolone

ARTHROPAN (Purdue Frederick)
Trade name for Choline Salicylate

ASCORBATE SODIUM
Trade names Ascorbin (Lakeside), Cenolate (Abbott) Natrascorb (U S Vitamin)
Administration Parenteral
Dosage form Ampule, 250 mg per ml

ASCORBIC ACID
Synonym Vitamin C, Cevitamic Acid

ASCORBIN (Lakeside)
Trade name for Ascorbate Sodium

ASPIDIUM OLEORESIN
Administration Oral
Dosage forms Capsule or emulsion of various sizes

ASPIRIN
Synonym for Acetylsalicylic Acid

ASTERIC (Brewer)
Trade name for Acetylsalicylic Acid

ASTEROL (Roche)
Trade name for Diamthazole

ASTRAFER (Astra)
Trade name for Iron Carbohydrate Complex

ATABRINE HCl (Winthrop)
Trade name for Quinacrine HCl

ATARAX (Roerig)
Trade name for Hydroxyzine HCl

ATOPHAN (Warner Chilcott)
Trade name for Cinchophen

ATRATAN (Irwin, Neisler)
Trade name for Atropine Tannate

ATROPINE SO_4
Administration Oral parenteral
Dosage forms Tablets and solutions in a large variety of forms and sizes

ATROPINE TANNATE
Trade name Atratan (Irwin, Neisler)
Administration Oral
Dosage form Tablet, 1 mg

AU^{198}
Synonym for Radio-Gold Colloid

AURCOLOID
Synonym for Radio Gold Colloid

AUREOMYCIN CALCIUM (Lederle)
Trade name for Chlortetracycline Calcium

AUREOMYCIN HCl (Lederle)
Trade name for Chlortetracycline HCl

AUROTHIOGLUCOSE
Trade name Solganal (Schering)
Administration Intramuscular
Dosage form Vials, 10, 50 100 mg per ml

AUROTHIOGLYCANIDE
Trade name Lauron (Endo)
Administration Intramuscular
Dosage form Vials, 50 and 150 mg per ml

AUROTHIOSULFATE SODIUM
Synonym for Gold Sodium Thiosulfate

AVEENO COLLOIDAL OATMEAL (Fougera)
Trade name for Oatmeal preparation

AVEENO SKIN CLEANSER (Fougera)
Detergent cleanser

AVERTIN (Winthrop)
Trade name for Tribromoethanol

AVLOSULFON (Ayerst)
Trade name for Dapsone

AZACYCLONOL HCl
Trade name Frenquel (Merrell)
Administration Oral
Dosage form Tablet, 20 mg

AZAMETHONIUM Br
Trade name Pendiomide (Ciba)
Administration Intravenous
Dosage form Ampule 50 mg per ml
Remarks Not available on drug market

AZAPETINE PO_4
Trade name Ilidar (Roche)
Administration Oral
Dosage form Tablet, 25 mg

AZASERINE
Synonym Serynl
Not available on commercial drug market

BETAXIN (Winthrop)
Trade name for Thiamine HCl

BETAZOLE HCl
Trade name Histalog (Lilly)
Administration Intramuscular, subcutaneous
Dosage form Ampule, 50 mg per ml

BETHANECHOL Cl
Trade name Urecholine Cl (Merck)
Administration Oral, subcutaneous
Dosage forms Tablet, 5 mg , ampule, 5 mg per ml

BEVATINE 12 (Dorsey)
Trade name for Cyanocobalamin

BEVIDORAL (Abbott)
Trade name for Intrinsic Factor with Vitamin B_{12}

BEVIDOX (Abbott)
Trade name for Cyanocobalamin

BEXITAB (Chicago)
Trade name for Intrinsic Factor with Vitamin B_{12}

B F I POWDER (Merck)
Fungicide mixture used largely in Europe

BIALLYLAMICOL HCl
Trade name Camoform HCl (Parke, Davis)
Administration Oral
Dosage form Tablet, 250 mg

BICHLORACETIC ACID
Administration Topical
Dosage form As such

BICHLORIDE OF MERCURY
Synonym for Mercuric Cl

BICILLIN (Wyeth)
Trade name for Benzathine Penicillin G

BICOL *(McNeil)*
Trade name for Ox Bile Extract

BIFACTON (Organon)
Trade name for Intrinsic Factor with Vitamin B_{12}

BILE EXTRACTIVES
Trade name Ketochol (Searle)
Administration Oral
Dosage form Tablet, 0 25 Gm

BILEIN (Abbott)
Trade name for Ox Bile Extract

BILRON (Lilly)
Trade name for Iron and Bile Salts

BIO DES (Grant)
Trade name for Diethylstilbestrol

BIOEPIDERM (Breon)
Trade name for Biotin

BIOPAR (Armour)
Trade name for Intrinsic Factor with Vitamin B_{12}

BIOPAR FORTE (Armour)
Trade name for Intrinsic Factor with Vitamin B_{12}

BIOTIN
Trade name Bioepiderm (Breon)
Administration Intramuscular
Dosage form Ampule, 0 25 mg per ml

BIPHETAMINE RESIN (Strasenburgh)
Trade name for Amphetamine Resin Complex

BISACODYL
Trade name Dulcolax (Geigy)
Administration Oral rectal
Dosage forms Tablets, 5 and 10 mg suppository, 10 mg

BISHYDROXYCOUMARIN
Trade name Dicumarol (Various manufacturers)
Administration Oral
Dosage forms Tablets, 25, 50 mg capsules 50, 100 mg

BISMUTH OCTYLOXYACETATE
Trade name Lipo Bismol (Parke Davis)
Administration Intramuscular
Dosage form Ampule, 100 mg , as Bismuth per ml

BISMUTH SUBCARBONATE
Administration Oral
Dosage form As such tablets of various sizes

BISMUTH SUBGALLATE
Administration Oral
Dosage form As such, tablets of various sizes

BISMUTH SUBNITRATE
Administration Oral
Dosage form As such tablets of various sizes

BISMUTH SUBSALICYLATE
Trade name Stabisol (Squibb)
Administration Intramuscular
Dosage form Ampule about 75 mg , as Bismuth, per ml

BENZAPAS (Smith Dorsey)
Trade name for Calcium Benzoyl Aminosalicylate

BENZATHINE PENICILLIN G
Trade names Bicillin (Wyeth) Neolin (Lilly) Permapen (Pfizer)
Administration Oral intramuscular
Dosage forms Tablets 100 000 200,000 units fluid, 60 000 units per ml ampules 300 000 600 000 and 1 200 000 units per ml

BENZEDREX (Smith, Kline & French)
Trade name for Propylhexedrine

BENZEDRINE SO_4 (Smith Kline & French)
Trade name for Amphetamine SO

BENZENE HEXACHLORIDE, GAMMA
Synonym for Gamma Benzene Hexachloride

BENZESTROL
Administration Oral vaginal intramuscular
Dosage forms Tablets 0 5 1 0 mg suppository 0 5 mg vial 5 mg per ml

BENZETHONIUM Cl
Trade names Anzol (Veltex) Phemerol Cl (Parke Davis)
Dosage forms Solution 0 1% 1% tincture 0 2%

BENZOCAINE (Merck)
Trade name for Ethyl Aminobenzoate

BENZODIOXANE
Synonym for Piperoxan HCl

BENZOIC ACID
Administration Topical
Dosage forms Various concentrations and physical forms are available

BENZOIN
Administration Inhalation
Dosage form Compound tincture

BENZONATATE
Trade name Tessalon (Ciba)
Administration Oral
Dosage form Perles 100 mg

BENZOTHIAZOLIUM I
Synonym for Dithiazanine I

BENZPYRINIUM Br
Trade name Stigmonene Br (Warner Chilcott)
Administration Intramuscular
Dosage form Ampule 2 0 mg per ml

BENZTROPINE METHANESULFONATE
Trade name Cogentin Methanesulfonate (Merck)
Administration Oral
Dosage form Tablet 2 mg

BENZYL ALCOHOL
Administration Topical
Dosage form Solutions 1 to 4%

BENZYL BENZOATE
Trade name Vanzoate (VanPelt & Brown)
Administration Topical
Dosage forms Emulsion 50% solution 20 %

BENZYLPHENYLCARBAMATE
Trade name Diphenan (Burroughs Wellcome)
Administration Oral
Dosage form Tablet 0 5 Gm

BEPHENIUM HYDROXYNAPHTHOATE
Synonym Alcopara
Not yet available on the commercial drug market

BERUBIGEN (Upjohn)
Trade name for Cyanocobalamin

BETA CONCEMIN (Merrell)
Trade name for Vitamin B Complex

BETADINE (Carbin & Conwell)
Trade name for Povidone Iodine Complex

BETALIN (Lilly)
Trade name for Vitamin B Complex

BETALIN S (Lilly)
Trade name for Thiamine HCl

BETALIN 12 (Lilly)
Trade name for Cyanocobalamin

BETANAPHTHOL BENZOATE
Administration Topical
Dosage form To be made up

BETAPLEXIN (Winthrop)
Trade name for Vitamin B Complex

BETA PYRIDYL-CARBINOL
Trade name Roniacol (Roche)
Administration Oral
Dosage forms Tablet 50 mg liquid about 12 5 mg per ml

BURO-SOL (Doak)
Trade name for Aluminum Acetate Solution

BUROW'S SOLUTION
Synonym for Aluminum Acetate Solution

BURSOLINE (Burnham)
Trade name for Diglycocoll Hydroiodide-Iodine

BUSULFAN
Trade name Myleran (Burroughs Wellcome)
Administration Oral
Dosage form Tablet, 2 mg

BUTABARBITAL SODIUM
Trade names Bubartal Sodium (Columbus), Butisol (McNeil)
Administration Oral
Dosage forms Capsule, 100 mg, tablets, 15, 30, 50, and 100 mg, elixir, 6 6 mg per ml

BUTACAINE SO_4
Trade name Butyn SO_4 (Abbott)
Administration Topical
Dosage form Solution, 2%

BUTAMBEN PICRATE
Trade name Butesin Picrate (Abbott)
Administration Topical
Dosage form Ointment, 1 5,000 and 1 100

BUTANEFRINE HCl (Winthrop)
Trade name for Ethylnorepinephrine HCl

BUTAZOLIDIN (Geigy)
Trade name for Phenylbutazone

BUTESIN PICRATE (Abbott)
Trade name for Butamben Picrate

BUTETHAL
Trade name Neonal (Abbott)
Administration Oral
Dosage form Tablet, 100 mg

BUTETHAMINE FORMATE
Trade name Monocaine Formate (Novocol)
Administration Intrathecal
Dosage form Solution, 5%, as such

BUTETHAMINE HCl
Trade name Monocaine HCl (Novocol)
Administration Parenteral
Dosage forms Ampules, 1 and 1 5% with Epinephrine

BUTISOL SODIUM (McNeil)
Trade name for Butabarbital Sodium

BUTYN SO_4 (Abbott)
Trade name for Butacaine SO_4

CADE OIL
Synonym for Juniper Tar

CADMIUM SULFIDE SUSPENSION
Trade name Capsebon (Pitman Moore)
Administration Topical
Dosage form Suspension, 1%

CAFFEINE AND SODIUM BENZOATE
Administration Subcutaneous, intramuscular, intravenous
Dosage form Ampule, 2 ml containing 0 5 Gm

CALAMINE
Administration Topical
Dosage forms Lotion and Ointment

CALCIFEROL
Synonyms Viosterol, Vitamin D_2
Trade names Deltalin (Lilly), Deratol (Brewer), Drisdol (Winthrop), Ertron (Whittier), Metadee (Merck), and many others
Administration Oral, parenteral
Dosage forms An endless variety

CALCIPHOS (*Bilhuber-Knoll*)
Trade name for Inositol Hexaphosphate

CALCIUM ACETYLSALICYLATE CARBAMIDE
Trade name Calurin (Smith Dorsey)
Administration Oral
Dosage form Tablet, 0 3 Gm

CALCIUM AMINOSALICYLATE
Trade name Parasal Calcium (Panray)
Administration Oral
Dosage form Tablet, 0 5 Gm

CALCIUM BENZOYL AMINOSALICYLATE
Trade name Benzapas (Smith Dorsey)
Administration Oral
Dosage forms Tablet, 0 5 Gm, powder, 4 Gm

CALCIUM CARBONATE
Administration Oral
Dosage form As such

CALCIUM Cl
Administration Intravenous, oral
Dosage forms Capsules, tablets, solution, 5%

CALCIUM CO_3 PRECIPITATED
Administration Oral
Dosage forms A large variety

CALCIUM DIOCTYL SULFOSUCCINATE
Trade name Doxical (Lloyd)
Administration Oral
Dosage form Capsules, 50 and 240 mg

BISMUTH TRIBROMOPHENATE
Trade name Xeroform (Warner)
Administration Oral
Dosage form As such

BISTRIUM Br (Squibb)
Trade name for Hexamethonium Br

BISTRIUM Cl (Squibb)
Trade name for Hexamethonium Cl

BI-SULFAZINE (Warren Teed)
Trade name for Dia Mer Sulfonamides

BISULFON *(Veltex)*
Trade name for Dia Mer Sulfonamides

BITHIONOL
Trade name Actamer (Monsanto)
Administration Topical
Dosage form As such

BITTER ORANGE OIL
Administration Oral
Dosage forms As such, tincture

BLOCKAIN (Breon)
Trade name for Propoxycaine HCl

BLOOD HUMAN WHOLE
Administration Intravenous
Dosage form As such

BLUE OINTMENT
Synonym for Mercurial Ointment Mild

BLUTENE Cl (Abbott)
Trade name for Tolonium Cl

BONADOXIN
Trade name for mixture of Meclizine HCl and Pyridoxine HCl

BONAMINE HCl (Pfizer)
Trade name for Meclizine HCl

BONINE (Pfizer)
New trade name for Meclizine HCl (Bonamine)

BORIC ACID
Administration Topical
Dosage forms Various concentrations and physical forms are available

BORNATE (Wyeth)
Trade name for Isobornyl Thiocyanoacetate

BOROFAX (Burroughs Wellcome)
Trade name for Boric Acid Cream

BRADOSOL Br (Ciba)
Trade name for Domiphen Br

BRAIN EXTRACT SOLUTION
Synonym Thromboplastin
Administration Topical oral subcutaneous, intravenous
Dosage form Vial 20 ml

BREWER S YEAST
Nonproprietary preparation of Vitamin B Complex

BRILLIANT GREEN
Administration Topical
Dosage forms As prescribed

BRISTAMIN (Bristol)
Trade name for Phenyltoloxamine D hydrogen Citrate

BROMISOVALUM
Trade name Bromural (Bilhuber Knoll)
Administration Oral
Dosage form Tablet 0 3 Gm.

BROMODIPHENHYDRAMINE HCl
Trade name Ambodryl HCl (Parke, Davis)
Administration Oral intravenous intramuscular
Dosage forms Capsule 25 mg vial 5 mg per ml

BROMSALIZOL (Hynson)
Trade name for Monobromosalicyl Alcohol

BROMSULPHALEIN (Hynson)
Trade name for Sulfobromophthalein Sodium

BROMURAL (Bilhuber Knoll)
Trade name for Bromisovalum

BRONKEPHRINE HCl (Breon)
Trade name for Ethylnorepinephrine HCl

BROXOLIN (Breon)
Trade name for Glycobiarsol

BUBARTAL SODIUM (Columbus)
Trade name for Butabarbital Sodium

BUCLIZINE HCl
Trade names Softran (Stuart) Vibazine (Pfizer)
Administration Oral
Dosage form Tablet, 50 mg

BUNAMIODYL
Trade name Orabilex (Fougera)
Administration Oral
Dosage form Capsule 0 75 Gm

CARB\CHOL
Synonym Carbamylcholine Cl
Trade name Doryl (Merck)
Administration Subcutaneous
Dosage form \mpule 0 25 mg per ml

CARBACRYLAMINE RESIN
Trade name Carbo-Resin (Lilly)
Administration Oral
Dosage form Powder 8 Gm

CARBAMIDE
Synonym for Urea

CARBAMIDOPHENYL DI (CARBOXYMETHYLTHIO) ARSENITE
Trade name Thiocarbarsone (Lilly)
Administration Oral
Dosage form Capsules, 25 50 mg

CARBAMYLCHOLINE CI
Synonym for Carbachol

CARBARSONE
Administration Oral, intravaginal
Dosage forms Capsule, 0 25 Gm tablets 0 05 and 0 25 Gm suppository, 0 13 Gm

CARBASED (Mallard)
Trade name for Acetylcarbromal

CARBAZOCHROME SALICYLATE
Trade names Adrenosem Salicylate (Massengill), Adrestat (Organon)
Administration Oral intramuscular
Dosage forms Tablets, 1 and 2 5 mg, syrup, 0 5 mg per ml, ampule, 5 mg per ml

CARBETAPENTANE CITRATE
Trade name Toclase (Pfizer)
Administration Oral
Dosage form Tablet, 25 mg

CARBETHYL SALICYLATE
Trade name Sal Ethyl Carbonate (Parke, Davis)
Administration Oral
Dosage form Tablet, 0 3 Gm

CARBINAZOLE (Denver)
Trade name for Imidazole

CARBOL-FUCHSIN PAINT
Trade name Carfusin (Rorer)
Administration Oral
Dosage form Paint, 0 3%

CARBOLIC ACID
Synonym for Phenol

CARBOMYCIN
Trade name Magnamycin (Pfizer)
Administration Oral
Dosage form Tablets 100 250 mg

CARBON DIOXIDE
Administration Inhalation
Dosage form Metal bottles, 5 to 10% in oxygen

CARBON TETRACHLORIDE
Administration Oral
Dosage form As such

CARBO RESIN (Lilly)
Trade name for Carbacrylamine Resin

CARBOXYLIC RESIN
Trade names Natrinil (National Drug), Resodec (Smith, Kline & French)
Administration Oral
Dosage form Powder 10 and 15 Gm

CARBROMAL
Trade name Adalin (Winthrop)
Administration Oral
Dosage form Tablet, 0 3 Gm

CARBUTAMIDE
Not available on the commercial drug market

CARDALIN (Irwin Neisler)
Each tablet contains Aminophylline, 0 325 Gm, Aluminum Hydroxide 0 16 Gm Ethyl Aminobenzoate, 0 03 Gm

CARDAMON
Administration Oral
Dosage form Elixir

CARDIAZOL (Bilhuber Knoll)
Trade name for Pentylenetetrazol

CARDIGIN (National Drug)
Trade name of Digitoxin

CARDILATE (Burroughs Wellcome)
Trade name for Erythrityl Tetranitrate

CARDIOGRAFIN (Squibb)
Trade name for Diatrizoate Methylglucamine

CARDIOMONE (Endo)
Trade name for Heart Muscle Extract

CARDRASE (Upjohn)
Trade name for Ethoxzolamide

CARFUSIN (Rorer)
Trade name for Carbol Fuchsin Paint

CARICIDE
Synonym for Diethylcarbamazine

CARINAMIDE
Synonym for Caronamide

CALCIUM GLUCONATE
Trade name Calglucon (Sandoz)
Administration Intravenous
Dosage forms 10 ml conta ning 1 Gm

CALCIUM GLUCONOGALACTOGLUCONATE
Trade name Neo Calglucon (Sandoz)
Administration Intravenous intramuscular, oral
Dosage forms Ampules 10 and 20% tablet, effervescent 4 Gm syrup

CALCIUM HYDROXIDE
Administration Oral
Dosage form Solution, 3 mg per ml

CALCIUM IODOSTEARATE
Trade name Stearodine (Parke Davis)
Administration Oral
Dosage form Tablet 10 mg Iod ne

CALCIUM KINATE GLUCONATE
Trade name Maxukal (Breon)
Administration Intravenous
Dosage form Ampule 50 mg Ca per ml

CALCIUM LACTATE
Administration Oral
Dosage form Tablets 0 3 0 6 Gm

CALCIUM LEVULINATE
Administration Intravenous intramuscular
Dosage form Ampules 100 mg per ml

CALCIUM MANDELATE
Trade name Camdelate (Abbott)
Administration Oral
Dosage form Tablet 0 5 Gm

CALCIUM PENICILLIN
Ava lable in ointments

CALCIUM PO
Administration Oral
Dosage form Powder

CALCIUM PO, TRIBASIC
Admin stration Oral
Dosage forms A variety of forms available

CALCIUM UNDECYLENATE
Trade name Caldesene (Maltb e)
Adm nistration Top cal
Dosage form Shaker 5%

CALDESENE (Maltbie)
Trade name for Calcium Undecylenate

CALGLUCON (Sandoz)
Trade name for Calcium Gluconate

CALOMEL
Synonym for Mild Mercurous Cl

CALURIN (Smith Dorsey)
Trade name for Calc um Acetylsalicylate Carbamide

CAMDELATE (Abbott)
Trade name for Calcium Mandelate

CAMOFORM (Parke Davis)
Trade name for B allylamicol HCl

CAMOFORM HCl (Parke, Davis)
Trade name for Biallylamicol HCl

CAMOQUIN HCl (Parke, Davis)
Trade name for Amodiaqu n HCl

CAMPHOR
Administration Intramuscular
Dosage form 10% in o l

CAMPOLON (Winthrop)
Trade name for Liver Injection Crude

CANTAXIN (Winthrop)
Trade name for Ascorb c Acid

CANTIL (Lakeside)
Trade name for Mepenzolate Methylbrom de

CAPROKOL (Merck)
Trade name for Hexylresorcinol

CAPRYLIC COMPOUND
Trade name Naprylate (Strasenburgh)
Administration Topical
Dosage forms Ointment 15% suppository 0 45 Gm

CAPSEBON (Pitman Moore)
Trade name for Cadmium Sulfide Suspension

CAPSICUM
Administration Oral
Dosage forms As such tincture

CAPTODIAMINE HCl
Trade name Suvren (Ayerst)
Administration Oral
Dosage forms Tablets 50 and 100 mg

CARAMIPHEN ETHANEDISULFONATE
Trade name Toryn (Smith Kline & French)
Administration Oral
Dosage forms Tablet 10 mg syrup 2 mg per ml

CARAMIPHEN HCl
Trade name Panparnit (Geigy)
Administration Oral
Dosage form Tablets 12 5 and 50 mg

CHINIOFON
Synonym Yatren
Trade names Anayodin (Bischoff), Quinoxyl (Burroughs Wellcome)
Administration Oral
Dosage form Tablets, 120, 250 mg

CHINOSOL (Jewell)
Trade name for Oxyquinoline SO_4

CHLORAL HYDRATE
Trade names Lorinal (Arnar-Stone), Noctec (Squibb), Somnos (Merck)
Administration Oral
Dosage forms Solutions of various strengths, capsules, 0 25 and 0 5 Gm

CHLORAMBUCIL
Trade name Leukeran (Burroughs Wellcome)
Administration Oral
Dosage form Tablet, 2 mg

CHLORAMINE-T
Trade name Chlorazene (Frost)
Dosage form As such tablet, 0 3 Gm

CHLORAMPHENICOL
Trade name Chloromycetin (Parke, Davis)
Administration Oral, intramuscular, topical
Dosage forms Capsules, 50, 100, 250 mg, vial, 1 0 Gm for dilution, variety of topical forms

CHLORAMPHENICOL SUCCINATE
Trade name Chloromycetin Succinate (Parke, Davis)
Administration Parenteral
Dosage form Vial, equivalent of 1 Gm Chloramphenicol in 10 ml

CHLORAZANIL
Trade name Daquin (Riker)
Not available on the commercial drug market

CHLORAZENE (Frost)
Trade name for Chloramine T

CHLORBUTANOL
Trade names Chloretone (Parke, Davis), Clortran (Wampole)
Administration Oral, inhalation
Dosage form Capsule, 0 3 Gm, inhalant

CHLORCYCLIZINE HCl
Trade names Di-Paralene HCl (Abbott), *Perazil (Burroughs Wellcome)*
Administration Oral
Dosage form Tablets, 25, 50 mg

CHLORESIUM (Rystan)
Trade name for Chlorophyll

CHLORETONE (Parke, Davis)
Trade name for Chlorbutanol

CHLORIODIZED OIL
Trade name Iodochlorol *(Searle)*
Administration Direct application
Dosage form Bottle, as such

CHLORISONDAMINE Cl
Trade name Ecolid Cl (Ciba)
Administration Oral
Dosage form Tablets, 25 and 50 mg

CHLORMERODRIN
Trade name Neohydrin (Lakeside)
Administration Oral
Dosage form Tablet, 18 3 mg

CHLORMEZANONE
Trade name Trancopal (Winthrop)
Administration Oral
Dosage form Capsule, 100 mg

CHLOROAZODIN
Trade name Azochloramid (Wallace & Tiernan)
Administration Topical
Dosage forms Ointment, 1 1,000, tablet, 0 55 Gm, solutions, 1:125 and 1 500 in Triacetin

CHLOROFORM
Administration Inhalation
Dosage form Bottles, as such

CHLOROFORM WATER
Administration Oral
Dosage form As such

CHLOROGUANIDE HCl
Synonym Proguanil HCl
Trade names Guanatol *HCl (Lilly)*, *Paludrine* HCl (Ayerst)
Administration Oral
Dosage form Tablets, 100, 300 mg

CHLOROMYCETIN (Parke, Davis)
Trade name *for Chloramphenicol*

CHLOROMYCETIN SUCCINATE (Parke, *Davis)*
Trade name for Chloramphenicol Succinate

CHLOROPHENOTHANE
Synonym DDT
Administration Topical
Dosage forms In a variety of mixtures with other agents

CHLOROPHYLL
Trade name Chloresium (Rystan) and others
Administration Topical
Dosage forms Ointment and solution, 0 2 to 0 5%

CARISOPRODOL
Trade names Rela (Schering) Soma (Wal lace)
Administrat on Oral
Dosage form Tablet 350 mg

CARNACTON (Cavendish)
Trade name for Diaphragm Muscle Extract
Administration Oral and parenteral

CAROID (Am Ferment)
Trade name for Papaya Enzyme

CARONAMIDE
Trade name Stat cin (Merck)
Administration Oral
Dosage form Tablet 0 5 Gm

CAROTENE
Synonym Prov tam n A
Administration Oral
Dosage form Solutions 5 000 7 500 U per ml

CARYOLYSINE HCl (Merck)
Trade name for Mechlorethamine HCl

CASCARA SAGRADA
Trade names Peristaltin (Ciba) Peristim (Mead Johnson)
Administration Oral
Dosage forms Extract flu dextract aromatic fluidextract

CASTOR OIL
Administration Oral
Dosage forms As such emulsions capsules

CATHOMYCIN SODIUM (Merck)
Trade name for Novobiocin Sodium

CATRON (Lakeside)
Trade name for β Phenylisopropyl Hydrazine

CAYTINE (Lakeside)
Trade name for Alpha (alpha methyl 3 4 methylenedioxyphenethylam no) methyl pyrocatechuyl Alcohol HCl

CCC
Synonym for Citrated Calcium Carb mide

CEBIONE (Merck)
Trade name for Ascorbic Acid

CEDILANID (Sandoz)
Trade name for Lanatoside C

CEDILANID D (Sandoz)
Trade name for Deslanoside

CEEPRYN Cl (Merrell)
Trade name for Cetyl Pyridinium Cl

CELLOTHYL (Warner Chilcott)
Trade name for Methylcellulose

CELLULOSE OXIDIZED
Trade names Hemo Pak (Johnson & John son) Oxycel (Parke Davis)
Administration Top cal
Forms Cotton gauze and cones of various s zes

CELONTIN (Parke Davis)
Trade name for Methsuximide

CENOLATE (Abbott)
Trade name for Ascorbate Sodium

CENTRINE (Bristol)
Trade name for Aminopentamide

CER O CILLIN POTASSIUM (Upjohn)
Trade name for Potassium Penicillin O

CERVILAXIN (National)
Trade name for Relaxin

CETAZINE (Bowman)
Trade name for Acet Dia Mer Sulfonamides

CETYL PYRIDINIUM Cl
Trade name Ceepryn Cl (Merrell)
Dosage forms Solutions and tinctures 1 200 1 500 1 1 000 suppos tories 1 1 000

CEVALIN (Lilly)
Trade name for Ascorb c Ac d

CEVEX (Walker)
Trade name for Ascorbic Acid

CEVITAMIC ACID
Synonym for Ascorbic Acid

CHALK
Administrat on Oral
Dosage form As such but usually in mixtures

CHARCOAL
Administration Oral
Dosage form Tablets as such

CHARCOAL ACTIVATED
Administration Oral
Dosage form Powder

CHELATE CALCIUM DISODIUM
Synonym for Edatham l Calcium D sod um

CHEL IRON (Kinney)
Trade name for Ferrochol nate

CHENOPODIUM OIL
Administration Oral
Dosage form Capsules 0 3 and 0 6 ml

CHOLINE SALICYLATE
Trade name Arthropan (Purdue Frederick)
Administration Oral
Dosage form Flavored solution, 0 9 Gm per 5 ml

CHOLINE THEOPHYLLINATE
Synonym for Oxtriphylline

CHOLOGRAFIN METHYLGLUCAMINE (Squibb)
Trade name for Iodipamide Methylglucamine

CHOLOGRAFIN SODIUM (Squibb)
Trade name for Iodipamide Sodium

CHONDODENDRON TOMENTOSUM
Trade name Intocostrin (Squibb)
Administration Intramuscular, intravenous
Dosage form Vial, 20 units per ml

CHORIOGONIN (Lakeside)
Trade name for Chorionic Gonadotropin

CHORIONIC GONADOTROPIN
Synonym *Growth hormone, Somatotropin*
Trade names Antuitrin (Parke, Davis), A P L (Ayerst), Choriogonin (Lakeside), Entromone (Endo), Follutein (Squibb), Gestasol (National), Korotrin (Winthrop), Pregnyl (Organon), Riogon (Breon)
Administration Intramuscular
Dosage forms Vials, 500, 1,000 I U per ml

CHOTHYN DIHYDROGEN CITRATE (Flint, Eaton)
Trade name for Choline Dihydrogen Citrate

CHROMIUM ANHYDRIDE
Administration Topical
Dosage form Solution, 20%

CHRYSAROBIN
Administration Topical
Dosage form Ointment, 6%

CHYMAR (Armour)
Trade name for Chymotrypsin

CHYMOTRYPSIN
Trade names Chymar (Armour), Cytolav (Armour), Enzeon (Breon)
Administration Oral, intramuscular
Dosage forms Capsule, 7 mg , vial, 500 U per ml

CIGNOLIN
Synonym for Dihydroxyanthranol

CILLORAL PENICILLIN (Bristol)
Trade name for Potassium Penicillin G

CINAPHYL (*Ascher*)
Trade name for Theophylline Sodium Glycinate

CINCHOPHEN
Trade name Atophan (Warner Chilcott)
Administration Oral
Dosage form Tablets, 0 3 and 0 5 Gm

CINCHOPHEN HYDRIODIDE
Trade name Oxyl-Iodide (Lilly)
Administration Oral
Dosage form Tablet, 0 3 Gm

CINNAMON OIL
Administration Oral
Dosage form As such

CITRATED CALCIUM CARBIMIDE
Synonym CCC
Trade name Temposil (Lederle)
Not available on the commercial drug market

CITROVORUM FACTOR
Synonym Folinic Acid
Trade name Leucovorin (Lederle)
Administration Intramuscular
Dosage form Ampule, 3 mg per ml

CLARIN (Leeming)
Trade name for Heparin Potassium

CLINOCAINE HCl
Trade name Naucaine (Taylor)
Administration Oral
Dosage forms Tablet, 120 mg , solution, 100 mg per ml

CLISTIN MALEATE (McNeil)
Trade name for Paracarbinoxamine Maleate

CLOPANE HCl (Lilly)
Trade name for Cyclopentamine HCl

CLORTRAN (Wampole)
Trade name for Chlorbutanol

CLYSEROL (Clyserol)
Trade name for Sodium PO_4 enema

CLYSMATHANE (Fleet)
Trade name for Theophylline Monoethanolamine enema

COAL TAR
Trade names Too numerous to list
Administration Topical
Dosage forms Various, 1 to 5%

COBRA VENOM PREPARATION
Trade names Cobroxin (Hynson), Nyloxin (Hynson)
Administration Intramuscular
Dosage form Ampules, several strengths

CHLOROPROCAINE HCl
Trade name Nesacaine HCl (Maltbie)
Administration Parenteral
Dosage form Ampules 1 2 and 3%

CHLOROPROCAINE PENICILLIN O
Trade name Depo Cer O Cillin Chloroprocaine (Upjohn)
Administration Intramuscular
Dosage form Ampule 300 000 units per ml

CHLOROQUINE PO
Trade name Aralen PO (Winthrop)
Administration Oral
Dosage form Tablet 0 25 Gm

CHLOROTHEN CITRATE
Trade name Tagathen Lederle)
Administration Oral
Dosage form Tablet 25 mg

CHLOROTHIAZIDE
Trade name Diuril (Merck)
Administration Oral
Dosage form Tablet 0 25 and 0 5 Gm

CHLOROTHIAZIDE SODIUM
Trade name Diuril Sodium (Merck)
Administration Intravenous
Dosage form Vial 0 5 Gm

CHLOROTHYMOL
Administration Topical
Dosage form Solution 0 05%

CHLOROTRIANISENE
Trade name Tace (Merrell)
Administration Oral
Dosage form Capsule containing 12 mg in oil

CHLORPACTIN (Guardian)
Trade name for Monoxychlorosene

CHLORPHENIRAMINE MALEATE
Trade names Chlor Trimeton Maleate (Schering) Teldrin (Smith Kline & French)
Administration Oral intramuscular subcutaneous
Dosage forms Tablets 4 8 and 12 mg solution 10 to 100 mg per ml

CHLORPHENOXAMINE HCl
Trade name Phenoxene (Pitman Moore)
Administration Oral
Dosage form Tablet 50 mg

CHLORPROMAZINE HCl
Trade name Thorazine (Smith Kline & French)
Administration Oral intravenous intramuscular rectal
Dosage forms Tablets 10 25 50 100 and 200 mg vial 25 mg per ml suppository 25 and 100 mg

CHLORPROPAMIDE
Trade name Diabinese (Pfizer)
Administration Oral
Dosage form Tablets 100 and 250 mg

CHLORQUINALDOL
Trade name Sterosan (Geigy)
Administration Oral
Dosage forms Cream ointment 3%

CHLORTETRACYCLINE CALCIUM
Trade name Aureomycin Calcium (Lederle)
Administration Oral
Dosage form Syrup about 30 mg per ml

CHLORTETRACYCLINE HCl
Trade name Aureomycin HCl (Lederle)
Administration Oral parenteral topical
Dosage forms Capsules 50 100 250 mg and a variety of other forms

CHLOR TRIMETON MALEATE (Schering)
Trade name for Chlorpheniramine Maleate

CHLORYLEN (Schering)
Trade name for Trichloroethylene

CHLORZOXAZONE
Trade name Paraflex (McNeil)
Administration Oral
Dosage form Tablet 250 mg

CHOLAN DH (Maltbie)
Trade name for Dehydrocholic Acid

CHOLARACE (Nepera)
Mixture of Ephedrine Pentobarbital and Theophylline

CHOLEDYL (Nepera)
Trade name for Oxtriphylline

CHOLESTEROL LOWERING FACTOR
Trade names Sass (Abbott) Arcofac (Armour)
Administration Oral
Dosage form As such

CHOLINE Cl
Administration Oral
Dosage form Solution 0 5 Gm per teaspoonful

CHOLINE DIHYDROGEN CITRATE
Trade name Chothyn Dihydrogen Citrate (Flint Eaton)
Administration Oral
Dosage forms Tablets 0 5 0 65 Gm capsules 0 25 0 5 Gm

CHOLINE GLUCONATE
Administration Oral
Dosage form Solution 50%

CORPUS LUTFUM
Trade name Lutein (Hynson), Progestone (Carnrick)
Administration Intramuscular
Dosage form Ampule, extractive of 0 45 Gm per ml

COR TAR QUIN (Dome)
Trade name for preparation containing Hydrocortisone 0 5% and 1 0%, Diiodohydroxyquin, 1% Liquor Carbonis Detergens, 2% in Acid Mantle vehicle

CORTATE (Schering)
Trade name for Desoxycorticosterone Acetate

CORT DOME (Dome)
Trade name for Hydrocortisone

CORTEF (Upjohn)
Trade name for Hydrocortisone

CORTEF ACETATE (Upjohn)
Trade name for Hydrocortisone Acetate

CORTICOTROPIN
Synonym ACTH
Trade names Acthar (Armour), Actrope (United), Cortrophin (Organon), Depo-ACTH (Upjohn), Solacthyl (Squibb)
Administration Intravenous intramuscular
Dosage forms Vials 10 15, 25, 40 units per ml gel, 20, 40, 80, 100 units per ml

CORTICOTROPIN ZINC HYDROXIDE
Trade name Cortrophin Zinc (Organon)
Administration Intramuscular
Dosage form Vial, 40 units per ml

CORTINAQ (Central)
Trade name for Desoxycorticosterone Acetate

CORTISONE ACETATE
Synonym Compound E
Trade names Cortogen Acetate (Schering), Cortone Acetate (Merck), Cortivite (United) Isopto Cortisone (Alcon Labs)
Administration Oral intramuscular, topical
Dosage forms Tablets 5, 25 mg , vial, 50 mg per ml ointments 0 5, 1 5, 2 5%

CORTIVITE (United)
Trade name for Cortisone Acetate

CORTOGEN ACETATE (Schering)
Trade name for Cortisone Acetate

CORTONE ACETATE (Merck)
Trade name for Cortisone Acetate

CORTRIL (Pfizer)
Trade name for Hydrocortisone

CORTRIL ACETATE (Pfizer)
Trade name for Hydrocortisone Acetate

CORTROPHIN (Organon)
Trade name for Corticotropin

CORTROPHIN ZINC (Organon)
Trade name for Corticotropin Zinc Hydroxide

COSA (Pfizer)
Trade name for Glucosamine

CORTARNINE CI
Trade name Stypticin (Merck)
Administration Topical, oral
Dosage form Solution, 30% as such

COTHERA (Ayerst)
Trade name for Dimethoxanate HCl

COTINAZIN (Pfizer)
Trade name for Isoniazid

COTOPHEROL (Endo)
Trade name for Tocopherols Mixed

COUMADIN SODIUM (Endo)
Trade name for Warfarin Sodium

COVICONE (Abbott)
Trade name for Silicone protective cream

CREAMALIN (Winthrop)
Trade name for Aluminum Hydroxide Gel

CREMODIAZINE (Merck)
Trade name for Sulfadiazine

CREOLIN PEARSON (Merck)
Trade name for Cresol

CRESATIN (Merck)
Trade name for Metacresylacetate

CRESOL
Trade names Creolin Pearson (Merck), Cresylone (Parke, Davis), Phenolor (Squibb)
Administration Topical
Dosage forms Various concentrations are available

CRESYLONE (Parke Davis)
Trade name *for Cresol*

CROTAMITON
Trade name Eurax (Geigy)
Administration Topical
Dosage forms Cream, 10%, lotion 10%

COBROXIN (Hynson)
Trade name for Cobra Venom Preparation

COCAINE
Administration Topical
Dosage form Solutions 1 to 4%

COD LIVER OIL
Administration Oral
Dosage forms As such emulsion 50%

CODEINE ALKALOID
Administration Oral
Dosage forms Varied

CODEINE PO
Administration Parenteral
Dosage forms Hypo tablets 15 30 and 60 mg

CODEINE SO
Administration Oral
Dosage forms Varied

CO DELTRA (Merck)
Trade name for Prednisone

COGENTIN METHANESULFONATE (Merck)
Trade name for Benztropine Methanesulfonate

COHISTINE (Pitman Moore)
Trade name for Methapyrilene HCl

CO HYDELTRA (Merck)
Trade name for Prednisolone

COLACE (Mead Johnson)
Trade name for Dioctyl Sodium Sulfosuccinate

COLCHICINE
Trade name Colchin (Parke Davis)
Administration Oral intravenous
Dosage forms Tablets 0 65 mg ampules 0 5 1 0 mg

COLCHIN (Parke Davis)
Trade name for Colchicine

COLLOIDAL GOLD
Trade name Rexaurum (Kahlenberg)
Administration Oral intravenous intramuscular
Dosage form Solution 1 mg per ml

COLOCYNTH
Administration Oral
Dosage form As such

COLOGEL (Lilly)
Trade name for Methylcellulose

COLPROSTERONE (Ayerst)
Trade name for Progesterone

COMBISTREP (Pfizer)
Trade name for Streptoduocin

COMPAZINE (Smith Kline & French)
Trade name for Prochlorperazine Dimaleate

COM PEN (C.S.C.)
Trade name for Procaine Penicillin G

COMPENAMINE (C.S.C.)
Trade name for l Ephenamine Penicillin G

COMPOCILLIN (Abbott)
Trade name for Hydrabamine Penicillin G

COMPOCILLIN V (Abbott)
Trade name for Phenoxymethyl Hydrabamine Penicillin

COMPOCILLIN VK (Abbott)
Trade name for Potassium Phenoxymethyl Penicillin

COMPOUND E
Synonym for Cortisone Acetate

COMPOUND ETHER SPIRIT
Administration Oral
Dosage form As such

COMPOUND F
Synonym for Hydrocortisone

CONESTRON (Wyeth)
Trade name for Estrogenic Substances Conjugated

CONGO RED
Administration Intravenous
Dosage form Ampule 10 mg per ml

CONTEBEN
Synonym for Amithiozone

COPARAFFINATE
Trade name Iso Par (Medical Chem)
Administration Topical
Dosage form Ointment 20%

COPPER COMPOUND
Trade name Cuprex (Merck)
Administration Topical
Dosage form Solution

COPSAMINE (Durst)
Trade name for Pyrilamine Maleate

CORAMINE (Ciba)
Trade name for Nikethamide

CYCLOPENTOLATE HCl
Trade name Cyclogyl HCl (Schieffelin)
Administration Topical
Dosage form Solutions 0 5 and 1 0%

CYCLOPROPANE
Synonym Trimethylene
Administration Inhalation
Dosage form Cylinders

CYCLOSERINE
Trade name *Seromycin (Lilly)*
Administration Oral
Dosage form Tablet 250 mg

CYCLOSPASMOL (Ives Cameron)
Trade name for Cyclandelate

CYCRIMINE HCl
Trade name Pagitane HCl (Lilly)
Administration Oral
Dosage form Tablets 1 25 and 2 5 mg

CYTELLIN (Lilly)
Trade name for Sitosterols

CYTOLAV (Armour)
Trade name for Chymotrypsin

CYTOMEL (Smith Kline & French)
Trade name for Sodium Liothyronine

DACTIL (Lakeside)
Trade name for Piperidolate HCl

DADEX *(Central)*
Trade name for Dextro Amphetamine SO

DAINITE (Irwin Neisler)
Each day tablet contains Sodium Pentobarbital 16 mg Aminophylline 0 2 Gm Ephedrine HCl 16 mg Ethyl Aminobenzoate 16 mg Aluminum Hydroxide 0 16 Gm Each night tablet contains Phenobarbital 25 mg Sodium Pentobarbital 32 *mg* Aminophylline, 0 25 Gm Ethyl Aminobenzoate 16 mg Aluminum Hydroxide 0 16 Gm

DALYDE (Hynson)
Trade name for D bromsalicylaldehyde

DANILONE (Schieffelin)
Trade name for Phenindione

DANTHRON
Synonym for Dihydroxyanthraquinone

DAPSONE
Trade name Avlosulfon (Ayerst)
Administration Oral
Dosage form Tablet

DAPTAZOLE
Synonym Amiphenazole
Not available on the commercial drug market

DAQUIN (Riker)
Trade name for Chlorazanil

DARA SUN SCREEN (Dara)
Isobutyl Para aminobenzoate cream

DARANIDE (Merck)
Trade name for Dichlorphenamide

DARAPRIM (Burroughs Wellcome)
Trade name for Pyrimethamine

DARBID *(Smith Kline & French)*
Trade name for Isopropamide I

DARICON (Pfizer)
Trade name for Oxyphencyclimine HCl

DARROW S SOLUTION (MODIFIED)
Synonyms Potassium and Sodium Chloride with Sodium Lactate Solution Potassic Saline
Trade name *Ionosol P S L Electrolyte Solution* (Abbott)
Administration Intravenous subcutaneous
Dosage form Bottles as such

DARSTINE Br (Merck)
Trade name for Mepiperphenidol Br

DARTAL HCl (Searle)
Trade name for Thiopropazate HCl

DARVON (Lilly)
Trade name for Dextro Propoxyphene HCl

DASEROL (Tyron)
Trade name for Mephenesin

DBI (U S Vitamin)
Trade name for Phenformin

DDT
Synonym for Chlorophenothane

DEANER (Riker)
Trade name for *Deanol Acetamidobenzoate*

DEANOL ACETAMIDOBENZOATE
Trade name Deaner (Riker)
Administration Oral
Dosage form Tablet 25 mg

DECADRON (Merck)
Trade name for *Dexamethasone*

DECAMETHONIUM Br
Trade name Syncurine (Burroughs Wellcome)
Administration Intravenous
Dosage form *Ampule 1 mg per ml*

CRYPTENAMINE
Trade name Unitensen (Irwin Neisler)
Administration Intramuscular
Dosage form Vial, 2 mg per ml

CRYPTENAMINE TANNATE
Trade name Unitensen Tannate (Irwin Neisler)
Administration Oral
Dosage form Tablet, 2 mg

CRYSTAMIN (Armour)
Trade name for Cyanocobalamin

CRYSTICILLIN (Squibb)
Trade name for *Procaine Penicillin G*

CRYSTODIGIN (Lilly)
Trade name for Digitoxin

CRYSTOIDS (Merck)
Trade name for Hexylresorcinol

CRYSTOSERPINE (*Smith Dorsey*)
Trade name for Reserpine

CUMERTILIN (Endo)
Trade name for Mercumatilin

CUMOPYRAN (Abbott)
Trade *name for* Cyclocumarol

CUPREX (Merck)
Trade name for Copper Compound

CYANOCOBALAMIN
Synonym Vitamin B_{12}
Trade names Berubigen (Upjohn) Betalin 12 (Lilly) *Bevatine 12* (Dorsey) Bevidox (Abbott) Biopar (Armour) *Crystamin* (Armour) Docibin (Walker) Dodecavite (U S Vitamin) Dodekroid (Riker) Plecyamin 12 (Plessner) Redisol (Merck) Rubramin (*Squibb*) Sytobex (Parke Davis V Tral (Flint Eaton) and *others*
Administration Intramuscular
Dosage form Vials *of many sizes from 15 to 1 000 mcg per ml*

CYCLAINE (Merck)
Trade name for Hexylcaine *HCl*

CYCLAMATE CALCIUM
Trade name Sucaryl Calcium (Abbott)
Administration Oral
Dosage form Solution 150 mg per ml

CYCLAMATE SODIUM
Trade name Sucaryl Sodium (Abbott)
Administration Oral
Dosage forms Tablet 125 mg solution 150 mg per ml

CYCLAMYCIN (*Wyeth*)
Trade name for Triacetyloleandomycin

CYCLANDELATE
Trade name Cyclospasmol (Ives Cameron)
Administration Oral
Dosage form Tablet 100 mg

CYCLIZINE
Trade name Marezine (Burroughs Wellcome)
Administration Oral rectal
Dosage forms Tablet 50 mg suppository 50 mg

CYCLIZINE *HCl*
Trade name Marezine HCl (*Burroughs* Wellcome)
Administration Oral subcutaneous
Dosage forms Tablet 50 mg solution 50 mg per ml

CYCLIZINE LACTATE
Trade name Marezine Lactate (Burroughs Wellcome)
Administration Intramuscular
Dosage form Ampule, 50 mg per ml

CYCLOBARBITAL CALCIUM
Trade name Phanodorn Calcium (Winthrop)
Administration Oral
Dosage form Tablet 0 2 Gm

CYCLOCUMAROL
Trade name Cumopyran (Abbott)
Administration Oral
Dosage form Tablets 25 50 mg

CYCLOGYL HCl (Schieffelin)
Trade name for Cyclopentolate HCl

CYCLOMETHYCAINE
Trade name Surfacaine (*Lilly*)
Administration Topical
Dosage forms A variety of forms

CYCLOPAL (Upjohn)
Trade name for Cyclopentenylallylbarbituric Acid

CYCLOPENTAMINE HCl
Trade name Clopane (Lilly)
Administration Intranasal intramuscular
Dosage forms Ampule, 25 mg in 1 ml solutions 0.5 and 1.0%

CYCLOPENTENYLALLYLBARBITURIC ACID
Trade name Cyclopal (Upjohn)
Administration Oral
Dosage form Capsules 50 and 150 mg

DESERPIDINE
Trade name Harmonyl (Abbott)
Administration Oral
Dosage form Tablets, 0 1, 0 25, 1 0 mg

DESICCATED BILE
Trade name Desicol (Parke, Davis)
Administration Oral
Dosage form Capsule, 0 325 Gm

DESICOL (Parke, Davis)
Trade name for Desiccated Bile

DESIVER (U S Vitamin)
Trade name for Vitamin B Complex

DESLANOSIDE
Trade name Cedilanid D (Sandoz)
Administration Intravenous intramuscular
Dosage form Ampules, 2 ml containing 0 4 mg , 4 ml containing 0 8 mg

DESOXYCORTICOSTERONE ACETATE
Trade names Cortate (Schering), Cortinaq (Central), Decortin (Schieffelin), Decosterone (Barry), Descotone (Merck), Doca Acetate (Organon), Percorten (Ciba), Steraq (Ascher)
Administration Intramuscular, subcutaneous
Dosage form Ampule, in oil or aqueous suspension, 5 mg per ml

DESOXYEPHEDRINE (Upjohn)
Trade name for Methamphetamine HCl

d DESOXYEPHEDRINE HCl
Synonym for Methamphetamine *HCl*

dl DESOXYEPHEDRINE HCl
Trade names Detrex (Mallard), Oxyfed (Cole), Methamphin (Rorer), Premodrin (Premo), Normadrine (VanPelt & Brown)
Administration Oral
Dosage form Tablets, 5 10 mg

DESOXYN (Abbott)
Trade name for Methamphetamine HCl

DESYPHED (Winthrop)
Trade name for Methamphetamine HCl

DETERGENT CLEANSERS
Acidolate (White), Almay Liquid Cleanser (Almay), Aquaphor (Duke), Aveeno Skin Cleanser (Fougera), Dermolate (White), Domolene (Dome), Lowila (Westwood), Mul Sol (Waynor), Nivea Cream (Duke), Nivea Skin Oil (Duke), pHisoderm (Winthrop)

DETREX (Mallard)
Trade name for dl Desoxyephedrine HCl

DEVEGAN (Winthrop)
Trade name of preparation containing principally Acetylaminohydroxyphenylarsonic Acid
Administration Intravaginal
Dosage forms Powder, 0 25 Gm suppository, 0 25 Gm of active arsenical

DEXAMETHASONE
Trade names Decadron (Merck), Deronil (Schering), Gammacorten (Ciba)
Administration Oral
Dosage form Tablet, 0 75 mg

DEXBROMPHENIRAMINE MALEATE
Trade name Disomer (White)
Administration Oral
Dosage forms Tablet, 2 mg sustained action tablet, 4, 6 mg syrup, 0 4 mg per ml

DEXEDRINE SO_4 (Smith, Kline & French)
Trade name for Dextro Amphetamine SO

DEXOVAL (Vale)
Trade name for Methamphetamine HCl

DEXSTIM (Central)
Trade name for Methamphetamine HCl

DEXTRAN
Trade names Expandex (C S C), Gentran (Baxter), Plavolex (Wyeth)
Administration Intravenous
Dosage forms Bottles, 6 and 12% solutions

DEXTRAN SO_4
Not available on commercial drug market

DEXTRO AMPHETAMINE SO_4
Trade names d Amfetasul (Pitman Moore), Amphex (Algro), Dexedrine SO_4 *(Smith, Kline & French)*
Administration Oral
Dosage form Tablets, 2 5 5, and 10 mg

DEXTRO CHLORPHENIRAMINE MALEATE
Trade name Polaramine (Schering)
Administration Oral
Dosage forms Tablet, 2 mg , Repetab 6 mg

DEXTROMETHORPHAN HBr
Trade names Dormethan *(Smith Dorsey)*, Romilar HBr (Roche)
Administration Oral
Dosage forms Tablet, 10 mg , syrup, 2 5 mg per ml

DEXTRO PROPOXYPHENE HCl
Trade name Darvon (Lilly)
Administration Oral
Dosage forms Tablets 30 and 60 mg

DECAPRYN (Merrell)
Trade name for Doxylamine Succinate

DECHOLIN (Ames)
Trade name for Dehydrocholic Acid

DECHOLIN SODIUM (Ames)
Trade name for Sodium Dehydrocholate

DECLOMYCIN (Lederle)
Trade name for Demethylchlortetracycline

DECORTIN (Schieffelin)
Trade name for Desoxycorticosterone Acetate

DEHYDROCHOLIC ACID
Trade names Cholan DH (Maltbie), Decholin (Ames), Procholon (Squibb)
Administration Oral
Dosage form Tablet 0 25 Gm

DELALUTIN (Squibb)
Trade name for Progesterone

DELATESTRYL (Squibb)
Trade name for Testosterone Enanthate

DELESTROGEN (Squibb)
Trade name for Estradiol Valerate

DELTA CORTEF (Upjohn)
Trade name for Prednisolone

DELTALIN (Lilly)
Trade name for Calciferol

DELTAMIDE (Armour)
Trade name for Quadri Sulfa Mixture

DELTASONE (Upjohn)
Trade name for Prednisone

DELTRA (Merck)
Trade name for Prednisone

DELVEX (Lilly)
Trade name for Dithiazanine I

DELVINAL (Merck)
Trade name for Vinbarbital Sodium

DEMECARIUM
Trade name Humorsol (Merck)
Administration Topical
Dosage form Dropper, 0 25% solution

DEMECOLCIN
Not available on commercial drug market

DEMEROL HCl (Winthrop)
Trade name for Meperidine HCl

DEMETHYLCHLORTETRACYCLINE
Trade name Declomycin (Lederle)
Administration Oral
Dosage form Capsule, 150 mg

DENYL (Premo)
Trade name for Diphenylhydantoin Sodium

DEPO ACTH (Upjohn)
Trade name for Corticotropin

DEPO CER O CILLIN CHLOROPROCAINE (Upjohn)
Trade name for Chloroprocaine Penicillin O

DEPO ESTRADIOL
Trade name for Estradiol Cyclopentylpropionate

DEPO HEPARIN (Upjohn)
Trade name for Heparin Sodium

DEPO PENICILLIN (Upjohn)
Trade name for Procaine Penicillin G

DEPO TESTOSTERONE (Upjohn)
Trade name for Testosterone Cyclopentylpropionate

DEPROPANEX (Merck)
Trade name for Pancreatic Extract
Administration Parenteral

DERATOL (Brewer)
Trade name for Calciferol

DERMA PACK SUN SCREEN (Doak)
Para aminobenzoic Acid cake

DERMATONE SOAP (Chicago Pharmacal)
Phenol soap

DERMOLATE (White)
Detergent cleanser

DERONIL (Schering)
Trade name for Dexamethasone

DES (Grant)
Trade name for Diethylstilbestrol

DESAMINE (Starr)
Trade name for Methamphetamine HCl

DESCOSTERONE (Barry)
Trade name for Desoxycorticosterone Acetate

DESCOTONE (Merck)
Trade name for Desoxycorticosterone Acetate

DESENEX (Wallace & Tiernan)
Trade name for Undecylenic Acid

DICODID (Bilhuber Knoll)
Trade name for Dihydrocodeinone Bitartrate

DICUMAROL (Various Manufacturers)
Trade name for Bishydroxycoumarin

DICURIN PROCAINE (Lilly)
Trade name for Merethoxylline Procaine

DICYCLOMINE HCl
Trade name Bentyl HCl (Merrell)
Administration Oral intramuscular
Dosage forms Capsule, 10 mg , syrup about 2 mg per ml , ampule, 10 mg per ml

DIENESTROL
Trade name Restrol (Central)
Administration Oral, subcutaneous, intramuscular
Dosage forms Tablets, 0 1, 0 5, 1 0, 1 5, and 5 0 mg vial, 5 mg per ml

DIETHOXYN
Trade name Intracaine HCl (Philadelphia Ampoule)
Administration Parenteral, topical
Dosage forms Ampule, 1 Gm ointments, 2%, 5%

DIETHYLCARBAMAZINE
Synonyms Banocide, Caricide
Trade name Hetrazan (Lederle)
Administration Oral
Dosage forms Tablet, 50 mg , syrup, 30 mg per ml

DIETHYL ETHER
Synonym for Ether

DIETHYL PROPANEDIOL
Trade name Prenderol (Squibb)
Administration Oral
Dosage form Tablet, 0 5 Gm

DIETHYLPROPION
Trade names Tenuate (Merrell), Tepanil (National)
Administration Oral
Dosage form Tablet, 25 mg

DIETHYLSTILBESTROL
Synonym Stilbestrol
Trade names Bio des (Grant), DES (Grant), Stilbetin (Squibb), and others
Administration Oral intramuscular, rectal
Dosage forms Tablets, 1 0 mg to 100 mg suppositories 0 1 to 0 5 mg , ampule, 25 mg per ml

DIETHYLSTILBESTROL DIPALMITATE
Trade name Stilpalmitate (Abbott)
Administration Intramuscular
Dosage form Ampule containing 7 or 14 mg in 1 ml of oil

DIETHYLST[illegible]
Trad[illegible]
Adm[illegible]
Dosage [illegible] Tablet, 50 mg , vial, 5 ml containing 0 25 Gm

DIETHYLSTILBESTROL DIPROPIONATE
Administration Intramuscular
Dosage form Ampules, 0 5, 1 0, and 5 0 mg per ml in oil

DIFFUSIN (Ortho)
Trade name for Hyaluronidase

DIGALEN (Roche)
Trade name for Partially Purified Digitalis Preparation

DIGALLOL TRIOLEATE LIQUID
Trade name Saf Tan (Texas Pharmacal)
Administration Topical
Dosage form As such

DIGICARDIUM (Rorer)
Trade name for Partially Purified Digitalis Preparation

DIGIFOLIN (Ciba)
Trade name for Partially Purified Digitalis Preparation

DIGIFORTIS (Parke, Davis)
Trade name for Partially Purified Digitalis Preparation

DIGIGLUSIN (Lilly)
Trade name for Partially Purified Digitalis Preparation

DIGILANID (Sandoz)
Administration Oral, rectal intravenous intramuscular
Dosage forms Tablet 0 33 mg suppository, 0 5 mg , vials, 30 and 90 ml , 0 33 mg per ml , ampules 2 and 4 ml , 0 2 mg per ml

DIGISEALS (Harvey)
Trade name for Crude Digitalis Leaf

DIGISIDIN (Winthrop)
Trade name for Digitoxin

DIGITALIN POTENT (Merck)
Trade name for Partially Purified Digitalis Preparation

DIGITALINE NATIVELLE (Varick)
Trade name for Digitoxin

DIGITALIS LEAF
Trade names Dig seals (Harvey), Digitora (Upjohn)
Administration Oral rectal
Dosage forms Tablets and capsules 0 5 and 1 0 Cat Unit, tincture, 1 Cat Unit per ml

DEXTROSF
Synonym Glucose
Administration Intravenous
Dosage forms 5 10 20 and 50% solutions in ampules

DEXTROSE AND SODIUM Cl INJECTION
Administration Intravenous subcutaneous
Dosage forms A variety of combinations

DFP
Synonym for Isoflurophate

DIABINESE (Pfizer)
Trade name for Chlorpropamide

DIACHYLON OINTMENT (Ulmer)
Trade name for Lead Oleate Ointment

DIAFEN (Schenley)
Trade name for Diphenylpyraline HCl

DIAGNEX (Squibb)
Trade name for Qu nine Carbacrylic Res n

DIAGNEX BLUE (Squibb)
Trade name for Azures n

DIAL (Ciba)
Trade name for Allobarbital

DIAL SOAP (Armour)
Hexachlorophene soap

DIA MER-SULFONAMIDES
Sy
Tr

Ac
Dosage forms Tablets 0 3 0 5 Gm solutions

DIAMINIDE (Merck)
Trade name for Pyrilamine Maleate

DIAMOX (Lederle)
Trade name for Acetazolamide

DIAMTHAZOLE HCl
Trade name Asterol (Roche)
Dosage forms Ointment t ncture powder 5%

DIASONE SODIUM (Abbott)
Trade name for Sulfoxone Sodium

DIASTASE
Trade name Taka Diastase (Parke, Davis)
Administration Oral
Dosage forms Capsule 0 16 Gm tablet 0 16 Gm l quid about 100 mg per ml

DIATRINE HCl (Warner)
Trade name for Methaphenilene HCl

DIATRIZOATE METHYLGLUCAMINE
Trade name Card ografin (Squ bb)
Administration Intravenous
Dosage form Ampule 85%

DIATRIZOATE SODIUM
Trade name Hypaque Sod um (Winthrop)
Administration Intravenous
Dosage form Ampule 50%

DIATRIZOATES SODIUM AND METHYLGLUCAMINE
Trade name Renografin (Squibb)
Administration Intravenous
Dosage form Ampules 30 60 76%

DIAZO OXO NORLEUCINE
Synonym DON
Not available on the commercial drug market

DIBENZYLINE (Smith Kline & French)
Trade name for Phenoxybenzamine HCl

DIBROMSALICYLALDEHYDE
Trade name Dalyde (Hynson)
Administration Top cal
Dosage forms Solution 0 5% ointment and powder 2%

DIBUCAINE HCl
Trade name Nupercaine HCl (Ciba)
Administration Parenteral topical
Dosage forms A variety of forms

DIBULINE SO_4 (Merck)
Trade name for D butol ne SO

DIBUTOLINE SO
Trade name Dibuline SO (Merck)
Administration Intramuscular subcutaneous
Dosage form Ampule 25 mg per ml

DICALCIUM PO
Administration Oral
Dosage form Tablet 0 5 Gm

DICHLORPHENAMIDE
Trade name Daranide (Merck)
Administration Oral
Dosage form Tablet 50 mg

DIIODOHYDROXYQUINOLINE
Synonym for Diiodohydroxyquin

DILABIL SODIUM (Breon)
Trade name for Sodium Dehydrocholate

DILANTIN SODIUM (Parke, Davis)
Trade name for Diphenylhydantoin Sodium

DILAUDID HCl (Bilhuber Knoll)
Trade name for Dihydromorphinone HCl

DIMENFORMON (Organon)
Trade name for Estradiol

DIMENFORMON BENZOATE (Organon)
Trade name for Estradiol Benzoate

DIMENFORMON DIPROPIONATE (Organon)
Trade name for Estradiol Dipropionate

DIMENHYDRINATE
Trade name Dramamine (Searle)
Administration Oral, rectal, intramuscular intravenous
Dosage forms Tablet, 50 mg , liquid, 3 mg per ml suppository, 100 mg , ampule, 50 mg per ml

DIMERCAPROL
Synonym BAL
Administration Intramuscular
Dosage form Ampule, 4 5 ml containing 150 mg in oil

DIMETANE (Robins)
Trade name for Parabromdylamine Maleate

DIMETHISOQUIN HCl
Trade name Quotane HCl (Smith, Kline & French)
Administration Topical
Dosage forms Ointment, lotion, 0 5%

DIMETHOXANATE HCl
Trade name Cothera (Ayerst)
Administration Oral
Dosage form Syrup, 5 mg per ml

DIMETHYLANE (National)
Trade name for Promoxolane

DIMETHYL TUBOCURARINE Cl
Trade name Mecostrin Cl (Squibb)
Administration Intravenous
Dosage form Vial, 1 mg per ml

DIMETHYL TUBOCURARINE I
Trade name Metubine I (Lilly)
Administration Intravenous
Dosage form Ampule, 0 5 and 1 0 mg per ml

DIMOTHYN (Flint, Eaton)
Trade name for Dihydroxy Aluminum Aminoacetate

DINACRIN (Winthrop)
Trade name for Isoniazid

[illegible]

(Squibb), Regutol (Pharmacs)
Administration Oral
Dosage forms Capsules 50 mg liquid 10 mg per ml , tablets, 50 and 100 mg

DIODOQUIN (Searle)
Trade name for Diiodohydroxyquin

DIODRAST (Winthrop)
Trade name for Iodopyracet

DIOGYN (Pfizer)
Trade name for Estradiol

DIOGYN B (Pfizer)
Trade name for Estradiol Benzoate

DIOGYN E (Pfizer)
Trade name for Ethinyl Estradiol

DIOGYNETS (Pfizer)
Trade name for Estradiol

DIOLANDRONE (Carnrick)
Trade name for Methandriol

DIOLOSTENE
Synonym for Methandriol

DIOLOXOL (Carnrick)
Trade name for Mephenesin

DIONOSIL (Glaxo)
Trade name for Propyliodine

DIOTHANE HCl (Merrell)
Trade name for Diperodon HCl

DIOVAC (Gray)
Trade name for Dioctyl Sodium Sulfosuccinate

DIOXYLINE
Trade name Paveril (Lilly)
Administration Oral
Dosage form Tablets, 100 and 200 mg

DI PARALENE HCl (Abbott)
Trade name for Chlorcyclizine HCl

DIPAXIN (Upjohn)
Trade name for Diphenadione

DIGITALIS PARTIALLY PURIFIED PREPARATIONS
Trade names Digalen (Roche) Digicardium (Rorer) Digifolin (Ciba) Digifortis (Parke Davis), Digiglusin (Lilly) Digitalin Potent (Merck), Digitol (Merck)
Administration Oral intramuscular
Dosage forms These vary with the particular preparation In general there are oral forms both solid and liquid and parenteral forms in ampules

DIGITOL (Merck)
Trade name for Partially Purified Digitalis Preparation

DIGITORA (Upjohn)
Trade name for Crude Digitalis Leaf

DIGITOXIN
Trade names Cardigin (National Drug) Crystodigin (Lilly) Digisidin (Winthrop Stearns) Digitaline Nativelle (Varick) Foxalin (Grant) Purodigin (Wyeth) Unidigin (Merrell)
Administration Oral parenteral
Dosage forms Tablets 0 05 0 1 0 15 and 0 2 mg ampules 0 2 mg per ml

DIGLYCOCOLL HYDROIODIDE IODINE
Trade name Bursoline (Burnham)
Dosage form Tablet equivalent of 16 4 mg Iodine

DIGOXIN
Trade name Lanoxin (Burroughs Wellcome)
Administration Oral intramuscular intravenous
Dosage forms Tablets 0 25 and 0 5 mg ampules 0 5 and 0 2 mg per ml

DIH[illegible]
T[illegible]
Ad[illegible] [illegible]muscular
Dosage forms Tablet 10 mg ampule 30 mg per ml

DIHYDROCODEINONE BITARTRATE
Trade name Dicodid (Knoll)
Administration Oral
Dosage form Tablet 5 mg

DIHYDR[illegible]
[illegible] (Sandoz)
Administration Sublingual intramuscular
Dosage forms Tablet 0 5 mg ampule 0 3 mg per ml

DIHYDROERGOTAMINE METHANE SULFONATE
Administration Parenteral
Dosage form Ampule 1 mg per ml

DIHYDROMORPHINONE HCl
Trade names Dilaudid HCl (Bilhuber Knoll) Hymorphan HCl (Endo)
Administration Intramuscular, subcutaneous oral
Dosage forms Vial 2 mg per ml tablets 1 2 3 4 mg

DIHYDROSTREPTOMYCIN
Administration Topical
Dosage forms Creams and ointments

DIHYDROSTREPTOMYCIN SO₄
Administration Intramuscular
Dosage forms Ampules 0 25 and 0 5 Gm per ml vials 1 and 5 Gm

DIHYDROTACHYSTEROL
Synonym Vitamin D_4
Trade name Hytakerol (Winthrop)
Administration Oral
Dosage forms Capsule 0 625 mg solution 1 25 mg per ml

DIHYDROXY ALUMINUM AMINOACETATE
Trade names Alminate (Bristol) Alzinox (Patch) Dimothyn (Flint Eaton) Doraxamin (Dorsey) Robalate (Robins)
Administration Oral
Dosage forms Tablet 0 5 Gm suspensions of various concentrations

DIHYDROXYANTHRANOL
Synonym Cignolin
Trade name Anthralin (Abbott)
Administration Topical
Dosage forms Ointments 0 1 0 25, 0 5 and 1 0%

DIHYDROXYANTHRAQUINONE
Synonym Danthron
Trade names Dorbane (Schenley) Istizin (Winthrop)
Administration Oral
Dosage form Tablet, 75 mg

DIHYDROXYCHOLANIC ACID
Trade name Droxolan (Breon)
Administration Oral
Dosage form Tablet 100 mg

DIHYPRYLONE
Trade name Sedulon (Roche)
Administration Oral
Dosage form Syrup 15 mg per ml

DIIODOHYDROXYQUIN
Synonym Diiodohydroxyquinoline
Trade names Diodoquin (Searle) Dorbane (Schenley) Floraquin (Searle) Moebiquin (C M C), Yodoxin (Glenwood)
Administration Oral intravaginal
Dosage forms Tablets 0 2 and 0 65 Gm powder 100 mg

D O F (Breon)
Trade name for Methamphetamine HCl

DOLITRONE (Merrell)
Not available on the commercial drug market

DOLOPHINE HCl (Lilly)
Trade name for Methadone HCl

DOME PASTE (Dome)
Zinc Oxide paste

DOMEBORO (Dome)
Trade name for Aluminum Acetate Solution

DOMICONE (Dome)
Silicone protective cream

DOMIPHEN Br
Trade name Bradosol Br (Ciba)
Administration Topical
Dosage form Lozenge 1 5 mg with 2 5 mg Benzocaine

DOMOLENE (Dome)
Detergent cleanser

DON
Synonym for Diazo Oxo Norleucine

DORAXAMIN (Dorsey)
Trade name for Dihydroxy Aluminum Aminoacetate

DORBANE (Schenley)
Trade name for Dihydroxyanthraquinone

DORIDEN (Ciba)
Trade name for Glutethimide

DORMETHAN (Smith Dorsey)
Trade name for Dextromethorphan Br

DORMIN (Dormin)
Trade name for Methapyrilene HCl

DORMISON (Schering)
Trade name for Methylparafynol

DORNAVAC (Merck)
Trade name for Pancreatic Dornase

DORSACAINE HCl (Dorsey)
Trade name for Benoxinate HCl

DORSAPHYLLIN (Dorsey)
Trade name for Theophylline Sodium Glycinate

DORSULFAS (Smith Dorsey)
Trade name for Acet Dia Mer Sulfonamides

DORYL (Merck)
Trade name for Carbachol

DOVE SOAP (Lever)
Superfatted soap

DOXICAL (Lloyd)
Trade name for Calcium Dioctyl Sulfosuccinate

DOXINATE (Lloyd)
Trade name for Dioctyl Sodium Sulfosuccinate

DOXOL (Blair)
Trade name for Dioctyl Sodium Sulfosuccinate

DOXYFED (Raymer)
Trade name for Methamphetamine HCl

DOXYLAMINE SUCCINATE
Trade name Decapryn (Merrell)
Administration Oral
Dosage forms Tablets, 12 5 and 25 mg syrup 1 25 mg per ml

DRAMAMINE (Searle)
Trade name for Dimenhydrinate

DRAMCILLIN (White)
Trade name for Potassium Penicillin

DRINALFA (Squibb)
Trade name for Methamphetamine HCl

DRISDOL (Winthrop)
Trade name for Calciferol

DROPCILLIN (White)
Trade name for Potassium Penicillin G

DROSTENE (Ascher)
Trade name for Methandriol

DROXOLAN (Breon)
Trade name for Dihydroxycholanic Acid

DULCOLAX (Geigy)
Trade name for Bisacodyl

DUOGRAFIN (Squibb)
Trade name for Methylglucamine Diatrizoate and Iodipamide

DUO STREP (Merck)
Trade name for Streptoduocin

DUO-SULFANYL (Arlington)
Trade name for Dia Mer Sulfonamides

DIPERODON HCl
Trade name Dothane HCl (Merrell)
Administration Topical
Dosage forms A variety of forms

DIPHASOL TESTOSTERONE (Kremers Urban)
Trade name for Testosterone

DIPHEMANIL METHYLSULFATE
Trade name Prantal Methylsulfate (Schering)
Administration Oral subcutaneous intramuscular topical
Dosage forms Tablet 100 mg ampule 25 mg per ml cream 20 mg per Gm

DIPHENADIONE
Trade name Dipaxin (Upjohn)
Administration Oral
Dosage form Tablets 1 and 5 mg

DIPHENAN (Burroughs Wellcome)
Trade name for Benzylphenylcarbamate

DIPHENHYDRAMINE HCl
Trade name Benadryl (Parke Davis)
Administration Oral parenteral topical
Dosage forms Capsule 50 mg fluid 2 5 mg per ml vials 10 mg per ml

DIPHENTOIN (Massengill)
Trade name for Diphenylhydantoin Sodium

DIPHENYLHYDANTOIN SODIUM
Synonym Phenytoin
Trade names Denyl (Premo) Dilantin Sodium (Parke Davis) Diphentoin (Massengill) and others
Administration Oral
Dosage form Capsule 100 mg

DIPHENYLPYRALINE HCl
Trade names Diafen (Schenley) Hispril (Smith Kline & French)
Administration Oral
Dosage form Tablet 2 mg

DIPYRONE
Trade names Methampyrone (Testagar) Narone (Ulmer) Nartate (Harvey), Novaldin (Winthrop)
Administration Oral intramuscular subcutaneous
Dosage forms Tablet 0 3 Gm ampule 0 5 Gm per ml

DIRNATE
Not available on commercial drug market

DISIPAL (Riker)
Trade name for Orphenadrine HCl

DISOMER (White)
Trade name for Dexbrompheniramine Maleate

DISTREPTOCIN SO (Lilly)
Trade name for Streptoduocin

DISTRYCIN (Squibb)
Trade name for Streptoduocin

DISULFIRAM
Trade name Antabuse (Ayerst)
Administration Oral
Dosage form Tablet 0 5 Gm

DISULFYN (Rorer)
Trade name for Dia Mer Sulfonamides

DITHIAZANINE I
Trade names Abminthic (Pfizer), Delvex (Lilly), Telmid (Lilly)
Administration Oral
Dosage forms Tablets 50 100 and 200 mg

DITUBIN (Schering)
Trade name for Isoniazid

DIUCARDYN (Ayerst)
Trade name for Mercaptomerin

DIUMFRIN (C D Smith)
Trade name for Mercurophylline

DIURETIN (Bilhuber Knoll)
Trade name for Theobromine and Sodium Salicylate

DIURIL (Merck)
Trade name for Chlorothiazide

DIURIL SODIUM (Merck)
Trade name for Chlorothiazide Sodium

DIURNAL-PENICILLIN (Upjohn)
Trade name for Procaine Penicillin G

DIVINYL OXIDE
Synonym for Vinyl Ether

DOCA ACETATE (Organon)
Trade name for Desoxycorticosterone Acetate

DOCIBIN (Walker)
Trade name for Cyanocobalamin

DODECAVITE (U S Vitamin)
Trade name for Cyanocobalamin

DODEKROID (Riker)
Trade name for Cyanocobalamin

ENZEON (Breon)
Trade name for Chymotrypsin

EPHEDRINE
Trade name Manadrin (Endo)
Administration Topical
Dosage form Aqueous or oily 1% solution

EPHEDRINE HCl
Synonym Racephedrine HCl
Trade names Efedron HCl (Hart), Ephetonin (Merck)
Administration Intramuscular or subcutaneous
Dosage forms Tablets, 30, 60 mg, ampule, 50 mg per ml

EPHEDRINE SO_4
Trade name Isofedrol (Blue Line)
Administration Oral, parenteral
Dosage forms Tablet, 25 mg, ampule, 25 mg

l-EPHENAMINE PENICILLIN G
Trade name Compenamine (C S C)
Administration Intramuscular
Dosage form Ampule, 300,000 units per ml

EPHETONIN (Merck)
Trade name for Ephedrine HCl

EPHYNAL (Roche)
Trade name for Tocopherols, Mixed

EPINEPHRINE
Trade name Adrenalin (Parke, Davis)
Administration Parenteral
Dosage form Ampule, 1 500, in oil

EPINEPHRINE BITARTRATE
Trade name Suprarenin (Winthrop)
Administration Parenteral
Dosage forms Ampules, 1 500 in oil and 1 1,000 in saline, bottles, 10 ml of 1 1,000

EPINEPHRINE HCl
Trade names Adrin (Merck), Adrenalin HCl (Parke, Davis), Episcorb (Paschall), Supranephrin (Rorer), Sus-Phrine (Brewer), Vasodrine (Premo)
Administration Subcutaneous, intravenous, intracardiac, inhalation
Dosage forms Ampule, vial, 1 1,000, 1 2,500, 1 10,000

EPINEPHRINE PO_4
Trade name Phosfo-Nefrin (Schieffelin)
Administration Subcutaneous
Dosage form Solution, 1 1,000

EPISCORB (Paschall)
Trade name for Epinephrine HCl

EPOXYMETHAMINE Br
Synonym for Methscopolamine Br

EPROLIN (Lilly)
Trade name for Tocopherols, Mixed

EPSILAN (Warren-Teed)
Trade name for Tocopherols, Mixed

EPSOM SALTS
Synonym for Magnesium SO_4

EQUANIL (Wyeth)
Trade name for Meprobamate

EQUINE GONADOTROPIN
Trade names Equinex (Ayerst), Gonadogen (Upjohn)
Administration Intramuscular
Dosage forms Ampules of varying dosage

EQUINEX (Ayerst)
Trade name for Equine Gonadotropin

EQUIPHYSIN (Harvey)
Trade name for Pituitary Gonadotropin

ERGOMAR (Nordson)
Trade name for Ergotamine Tartrate

ERGOMETRINE MALEATE
Synonym for Ergonovine Maleate

ERGONOVINE MALEATE
Synonyms Ergometrine, Ergostetrine, Ergotocine
Trade name Ergotrate Maleate (Lilly)
Administration Oral, intravenous, intramuscular
Dosage forms Tablet, 0 2 mg, ampule, 0 2 mg per ml

ERGONOVINE TARTRATE
Trade name Basergin (Sandoz)
Administration Oral, intramuscular, intravenous, subcutaneous
Dosage forms Ampule, 0 2 mg per ml, tablet, 0 25 mg

ERGOSTETRINE
Synonym for Ergonovine

ERGOT
Trade name Ergotole (Merck)
Administration Oral, intramuscular
Dosage forms Extract, fluidextract

ERGOTAMINE TARTRATE
Trade names Ergomar (Nordson), Gynergen (Sandoz)
Administration Oral, subcutaneous, intramuscular
Dosage forms Tablet, 1 mg, ampule, 0 5 mg per ml

DUOZINE (Abbott)
Trade name for Dia Mer Sulfonamides

DURABOLIN (Organon)
Trade name for Nandrolone Phenprop onate

DURACILLIN (Lilly)
Trade name for Proca ne Pen cill n G

DYCLONE (Pitman Moore)
Trade name for Dyclonine HCl

DYCLONINE HCl
Trade name Dyclone (Pitman Moore)
Admini tration Topical
Dosage forms Cream 1% solut on 0 5%

DYLEPHRIN (Irwin Neisler)
Aerosol spray Ep nephr ne HCl 2 5% Atro pine SO 0 5%

ECHOTHIOPHATE
Synonym Phospholine I
Not ava lable on commercial drug market

ECOFROL (Breon)
Trade name for Tocopherols M xed

ECOLID Cl (Ciba)
Trade name for Chlorisondamine Cl

ECOTRIN (Smith Kline & French)
Trade name for Acetylsal cyl c Acid

ECTYLUREA
Trade name Nostyn (Ames)
Administration Oral
Dosage form Tablet 0 3 Gm

EDATHAMIL CALCIUM DISODIUM
Synonyms EDTA Calcium Disodium Che late
Trade names Versenate Calcium Disod um (Riker)
Administration Intravenous
Dosage form Ampule 200 mg per ml

EDATHAMIL DISODIUM
Trade names Endrate (Abbott) Sod um Versenate (Riker)
Administration Intravenous
Dosage form Ampule 3 Gm n 0 ml

EDIOL (Schenley)
Trade name for Fat Emuls on Oral

EDROPHONIUM Cl
Trade name Tensilon Cl (Roche)
Administration Intravenous
Dosage form Ampule 10 mg per ml

EFEDRON HCl (Hart)
Trade name for Ephedrine HCl

EFROXINE (Maltbie)
Trade name for Methamphetamine HCl

ELATFRIN
Administration Oral
Dosage form As such

ELIPTEN
Not ava lable on commercial drug market

ELKOSIN (Ciba)
Trade name for Sulfisomid ne

ELORINE SO (Lilly)
Trade name for Tricyclamol SO

EMETINE BISMUTH I
Administration Subcutaneous intramuscular
Dosage forms Var ous forms

EMETINE HCl
Administration Subcutaneous intramuscular
Dosage forms Var ous forms

EMETROL (Kinney)
Trade name for Phosphorated Carbohydrate Solut on

EMULSION BASE (Almay)
O ntment base

ENDOTHYRIN (Harrower)
Trade name for Thyroglobul n

ENDRATE (Abbott)
Trade name for Edathamil D sodium

ENELONE (Arlington)
Trade name for Pregnenolone

ENKIDE (Brewer)
Trade name for Potassium I

ENOVID (Searle)
Trade name for Norethynodrel

ENTERO VIOFORM (Ciba)
Trade name for Iodochlorhydroxyquin

ENTODON (Winthrop)
Trade name for Prop odal

ENTROMONE (Endo)
Trade name for Chor on c Gonadotropin

ENTSUFON
Trade name pH soderm (Winthrop)
Administration Top cal
Dosage form As such

ENZACTIN (Ayerst)
Trade name for Triacetin

ESTRIFOL (Premo)
Trade name for Estrogenic Substances, Conjugated

ESTRIOL
Trade name Theelol (Parke, Davis)
Administration Oral
Dosage form Capsule, 0 24 mg

ESTROGENIC SUBSTANCES, CONJUGATED
Trade names Amnestrogen (Squibb), Conestron (Wyeth), Estrifol (Premo), Hormesteral (Miller), Konogen (Lilly), Premarin (Ayerst)
Administration Oral
Dosage forms Tablets, 0 3, 0 6, 1 25, and 2 5 mg liquid, 0 16 mg per ml

ESTRONE
Trade names Amniotin (Squibb), Estru- [illegible] (C D [illegible] n [illegible] d

ESTRUGENONE (Kremers Urban)
Trade name for Estrone

ESTRUSOL (C. D Smith)
Trade name for Estrone

ETALATE (Parke, Davis)
Trade name for Ethylamine Oleate

ETAMON Cl (Parke, Davis)
Trade name for Tetraethylammonium Cl

ETHAVERINE HCl
Administration Oral, intravenous
Dosage forms Tablet, 32 mg , ampule, 20 mg per ml

ETHCHLORVYNOL
Trade name Placidyl (Abbott)
Administration Oral
Dosage form Capsules 100, 200, and 500 mg

ETHER
Synonyms Ethyl Ether, Diethyl Ether
Administration Inhalation
Dosage form Containers as such

ETHINAMATE
Trade name Valmid (Lilly)
Administration Oral
Dosage form Tablet 0 5 Gm

ETHINORAL (C. D Smith)
Trade name for Ethinyl Estradiol

ETHINYL ESTRADIOL
Trades names Diogyn E (Pfizer), Esteed (Warren Teed), Estinyl (Schering), Ethinoral (C D Smith), Eticylol (Ciba), Inestra (Merck), Lynoral (Organon), Oradiol (VanPelt & Brown), Orestralyn (McNeil)
Administration Oral
Dosage forms Tablets, 0 01, 0 02, 0 05, 0 5 mg liquid, 0 004, 0 0075 mg per ml

ETHIODOL (Fougera)
Trade name for Ethyl Ester Iodinated Poppy Seed Oil

ETHISTERONE
Trade names Lutocylol (Ciba), Ora Lutin (Parke Davis), Pranone (Schering), Progestoral (Organon), Proluton C (Schering), Trosinone (Abbott), and others
Administration Oral, buccal
Dosage form Tablets, 5 10, 25 mg

ETHOHEPTAZINE CITRATE
Trade name Zactane (Wyeth)
Administration Oral
Dosage form Tablet, 75 mg

ETHOHEXADIOL
Administration Topical
Dosage form As such

ETHOPROPAZINE HCl
Trade name Parsidol (Warner Chilcott)
Administration Oral
Dosage form Tablets, 10, 50, and 100 mg

ETHOTOIN
Trade name Peganone (Abbott)
Administration Oral
Dosage form Tablets, 0 25 and 0 5 Gm

ETHOXAZENE
Trade name Serenium (Squibb)
Administration Oral
Dosage form Tablet, 100 mg

ETHOXZOLAMIDE
Trade name Cardrase (Upjohn)
Administration Oral
Dosage form Tablet, 125 mg

ETHYLAMINE OLEATE
Trade name Etalate (Parke, Davis)
Administration Intravenous
Dosage form Ampule, 5%

ETHYL AMINOBENZOATE
Trade names Anesthesin (Abbott), Benzocaine (Merck)
Dosage forms Various forms and concentrations from 1 to 20% available

FRGOTOCINE
Synonym for Ergonov ne

ERGOTOLE (Merck)
Trade name for Ergot Ex ract

ERGOTRATF MALFATE (Lilly)
Trade name for Ergonov ne Maleate

ERTRON (Whittier)
Trade name for Calc ferol

ERYTHRITYL TETRANITRATE
Trade name Card late (Burroughs Well come) Erythrol Tet an trate (Merck)
Adm n s at on Oral
Dosage form Tablets 15 and 30 mg

ERYTHROCIN (Abbott)
Trade name for Erythromy n

ERYTHROCIN LACTOBIONATE (Abbott)
Trade name for Erythromyc n I actob ona e

ERYTHROCIN STEARATE (Abbott)
Trade name for Erythromyc n Steara e

ERYTHROL TETRANITRATE (Merck)
Trade name for Erythr tyl Te ran trate

ERYTHROMYCIN
T ade name Erythroc n (Abbott Ilotycin (L l y)
Adm n strat on Oral top cal
Do age fo m Tablets 100 and 200 mg

ERYTHROMYCIN LACTOBIONATE
Trade name Erythroc n Lactob onate (Ab bott)
Adm n t at on Parenteral top cal
Dosage form Ampule 30 mg per ml

ERTHROMYCIN PROPIONATE
Trade name Ilosone (L lly)
Adm n t at o Oral
Do age fo m Tablets 125 and 250 mg

ERYTHROMYCIN STEARATE
Trade name Ery hroc n S earate (Abbott
Adm n t at on Oral
Do age fo m Tablets 100 50 mg

ESCHATIN (Parke Davis)
Trade name for Adrenal Cortex Extrac

ESERINE SALICYLATE
Synonym for Physost gm ne

ESIDRIX (C ba)
Trade name for Hydrochloro h az de

ESKACILLIN (Sm th Kl ne & French)
Trade name for Proca ne Pen c ll n G

ESKADIAMER (Sm th Kline & French)
Trade name for D a Mer Sulfonamides

FSKASERP (Smith Kl ne & French)
Trade name for Reserp ne

ESOMID Cl (Ciba)
Trade name for Hexamethonium Cl

ESORB (Wyeth)
Trade name for Tocopherols M xed

ESTEED (Warren Teed)
Trade name for Eth nyl Estrad ol

ESTINYL (Schering)
Trade name for Eth nyl Estrad ol

ESTRADIOL
T ade nan es Aquad ol (National Drug) Aqu ol (Estro) D ogyn (Pfizer) D ogyne s (Pfizer) D menformon (Organon) Estral d ne (Rorer) Ovocyl n (C ba) Progynon (Schering)
Ad n nis ation Oral vaginal ntramuscular
Dosage forms Tablets 0 1 0 2 0 5 mg pellet 25 mg vials 0 25 1 0 mg per ml

ESTRADIOL BENZOATE
T ade names D menformon Benzoate (Or ganon) D ogyn B (Pfizer) Ovocyl n Ben zoate (C ba) Progynon B (Schering) Solestro (Merck)
Adm n trat on Intramuscular
Do age form Ampules 0 166 0 33 1 66 and 2 0 mg per ml n o l

ESTRADIOL CYCLOPENTYLPROPIO NATE
T ade name Depo-Estrad ol (Upjohn)
Adm n st at on Intramuscular
Do age fo m V als 1 and 5 mg per ml

ESTRADIOL DIPROPIONATE
T ade names D menformon D prop onate

FSTRADIOL VALERATE
Trade name Delestrogen (Squ bb)
Adm n trat on Intramuscular
Do age form V als 10 mg per m l

ESTRADURIN (Ayerst)
Trade name for Polyestrad ol PO

ESTRALDINE (Rorer)
Trade name for Estrad ol

ESTRATE (Lakes de)
Trade name for Alphaes rad ol Triacetate

FERRIC OXIDES
Used in Neocalamine and other protectives

FERROCHOLINATE
Synonym Iron Choline Citrate
Trade names Chel Iron (Kinney), Ferrolip (Flint, Eaton)
Administration Oral
Dosage forms Tablet 1 Gm (120 mg Fe) syrup 16 mg Fe per ml

FERROLIP (Flint, Eaton)
Trade name for Ferrocholinate

FERRONORD (Nordmark)
Trade name for Aminoacetic Ferrous SO_4 Complex

FERROPYRIN (Bilhuber Knoll)
Trade name for Phenyldimethylpyrazolon Ferric Cl

FERROUS CO_3
Trade name Fecarb (Ayerst)
Administration Oral
Dosage form Tablet, 200 mg

FERROUS FUMARATE
Trade names Firon (Beard), Fumeron (Standex), Toleron (Mallinckrodt)
Administration Oral
Dosage form Tablets, 200 and 350 mg

FERROUS GLUCONATE
Trade names Fergon (Winthrop) Irox (Cole), Nionate (Nion)
Administration Oral
Dosage forms Tablets, 0 16 and 0 32 Gm elixir 60 mg per ml

FERROUS LACTATE
Administration Oral
Dosage form As prescribed

FERROUS SO_4
Trade names Feosol (Smith, Kline & French) Ferralyn (Lannett), Sulferrous (Chicago)
Administration Oral
Dosage forms Tablets capsules, 0 2 and 0 3 Gm

FIBRIN FOAM
Administration Topical
Dosage form As such

FIBRINOGEN (BOVINE)
Trade name Fibrogen (Merrell)
Administration Oral
Dosage form Vial 1 5% fibrinogen and 0 5% cephalin

FIBRINOGEN (HUMAN)
Trade name Parenogen (Cutter)
Administration Intravenous
Dosage form Vial, 1 Gm

FIBROGEN (Merrell)
Trade name for Fibrinogen (Bovine)

FIBROLYSIN, HUMAN
Trade name Actase (Ortho)
Administration Intravenous
Dosage form Vial, 50,000 units

FIRON (Beard)
Trade name for Ferrous Fumarate

FLAVAXIN (Winthrop)
Trade name for Riboflavin

FLAXEDIL (Lederle)
Trade name for Gallamine Triethiodide

FLEET ENEMA (Fleet)
Trade name for Sodium PO_4 solution

FLEXIN (McNeil)
Trade name for Zoxazolamine

FLO CILLIN (Bristol)
Trade name for Procaine Penicillin G

FLORANTYRONE
Trade name Zanchol (Searle)
Administration Oral
Dosage form Tablet, 250 mg

FLORAQUIN (Searle)
Trade name for Diodoquin

FLORINEF (Squibb)
Trade name for Fludrocortisone Acetate

FLOROPRYL (Merck)
Trade name for Isoflurophate

FLUDROCORTISONE ACETATE
Synonym Fluorohydrocortisone Acetate
Trade names Alflorone (Merck), F Cortef (Upjohn), Florinef (Squibb)
Administration Oral, topical
Dosage forms Tablets, 0 1, 1 0 mg ointment, lotion 0 05, 0 1, 0 2%

FLUMETHIAZIDE
Trade name Ademol (Squibb)
Administration Oral
Dosage form Tablet, 500 mg

FLUORESCEIN SODIUM
Administration Topical
Dosage form Solution 2%

ETHYL BISCOUMACETATE
Trade name Tromexan Ethyl Acetate (Geigy)
Administration Oral
Dosage form Tablets scored 150 and 300 mg

ETHYL CHLORIDE
Administration Inhalation
Dosage form Spray bottles as such

ETHYLDIMETHYLAMMONIUM Br
Trade name Ambutonium Br (Wyeth)
Administration Oral
Dosage form Tablet 10 mg

ETHYLENE
Administration Inhalation
Dosage form Cylinders as such

ETHYLEPHEDRINE HCl
Trade name Nethamine HCl (Merrell)
Administration Oral
Dosage form Capsule 25 mg tablet 50 mg

ETHYL ESTER IODINATED POPPY SEED OIL
Trade name Ethiodol (Fougera)
Administration Instillation
Dosage form Ampule as such

ETHYL ETHER
Synonym for Ether

ETHYL IODOPHENYLUNDECYLATE
Synonym for Iophendylate

ETHYLNOREPINEPHRINE HCl
Trade name Butanefrine HCl (Winthrop) Bronkephrine HCl (Breon)
Administration Subcutaneous intramuscular
Dosage form Vial 2 mg per ml

ETICYLOL (Ciba)
Trade name for Ethinyl Estradiol

E-TOPLEX (U S Vitamin)
Trade name for Tocopherols Mixed

EUCALYPTOL
Administration Topical
Dosage form As such

EUCATROPINE HCl
Trade name Euphthalmine HCl (Warner Chilcott)
Administration Topical
Dosage form As such

EUPHTHALMINE HCl (Warner Chilcott)
Trade name for Eucatropine HCl

EUQUININE
Synonym for Quinine Ethylcarbonate

EURAX (Geigy)
Trade name for Crotamiton

EURESOL (Bilhuber Knoll)
Trade name for Resorcinol Monoacetate

EVANS BLUE
Administration Intravenous
Dosage form Ampule 0.5% further diluted

EVIPAL SODIUM (Winthrop)
Trade name for Hexobarbital Sodium

EVRONAL SODIUM (Evron)
Trade name for Secobarbital Sodium

EXORBIN (Ayerst)
Trade name for Polyamine Methylene Resin

EXPANDEX (CSC)
Trade name for Dextran

FACTOR T
Not available on the commercial drug market

FAT EMULSION ORAL
Trade name Ediol (Schenley)
Administration Oral
Dosage form Emulsion 50% fat 12.5% sucrose

F CORTEF (Upjohn)
Trade name for Fludrocortisone Acetate

FECARB (Ayerst)
Trade name for Ferrous CO_3

FEDU
Designation for Fleet Enema Disposable Unit

FEMERGIN
Synonym for Ergotamine Tartrate

FENDON (American Pharmaceutical)
Trade name for Acetaminophen

FEOSOL (Smith Kline & French)
Trade name for Ferrous SO_4

FERGON (Winthrop)
Trade name for Ferrous Gluconate

FERRALYN (Lannett)
Trade name for Ferrous SO_4

FERRIC GLYCEROPHOSPHATE
Administration Oral
Dosage form As prescribed

FERRIC HYPOPHOSPHATE
Administration Oral
Dosage form As prescribed

GALLAMINE TRIETHIODIDE
Trade name Flaxedil (Lederle)
Administration Intravenous
Dosage form Vial, 20 mg per ml

GALLOGEN (Massengill)
Trade name for p-Tolylmethylcarbinol Mono-d-camphorate Diethanolamine

GALLOTANNIC ACID
Synonym for Tannic Acid

GAMMA BENZENE HEXACHLORIDE
Trade names Gexane (Strasenburgh), Kwell (Reed & Carnrick)
Administration Topical
Dosage forms Ointment and liquid, 1%

GAMMACORTEN (Ciba)
Trade name for Dexamethasone

GAMOPHEN (Ethicon)
Trade name for Hexachlorophene

GAMOPHEN SURGICAL SOAP (*Ethicon*)
Hexachlorophene soap

GANTRISIN (Roche)
Trade name for Sulfisoxazole

GANTRISIN ACETYL (Roche)
Trade name for Acetyl Sulfisoxazole

GANTRISIN DIETHANOLAMINE (Roche)
Trade name for Sulfisoxazole Diethanolamine

GASTRIC MUCIN
Administration Oral
Dosage form As such

GASTROGRAFIN (Squibb)
Trade name for Methylglucamine Diatrizoate

GASTULORIC (Warren-Teed)
Trade name for Glutamic Acid HCl

GELATIN SOLUTION, PURIFIED
Synonym Oxypolygelatin
Trade name Plazmoid (Upjohn)
Administration Intravenous
Dosage form Bottle, 50 mg per ml

GELATIN SPONGE, ABSORBABLE
Trade name Gelfoam (Upjohn)
Administration Topical
Dosage forms Powder, sponges, compressed sponges, packs, cones of various sizes

GELFOAM (Upjohn)

GELUSIL (Warner Chilcott)
Trade name for Magnesium Trisilic
Aluminum Hydroxide

GEMONIL (Abbott)
Trade name for Metharbital

GENTERSAL (Ortho)
Trade name for Methylrosaniline

GENTIAN
Administration Oral
Dosage forms As such, elixir, extrac
extract, compound tincture

GENTIAN VIOLET
Synonym for Methylrosaniline Cl

GENTRAN (Baxter)
Trade name for Dextran

GESTASOL (National)
Trade name for Chorionic Gonadotrop

GEXANE (Strasenburgh)
Trade name for Gamma Benzene He
ride

GINGER
Administration Oral
Dosage form Fluidextract

GITALIGIN (*White*)
Trade name for Gitalin

GITALIN
Trade name Gitaligin (White)
Administration Oral
Dosage form Tablet, 0.5 mg

GLARUBIN (Massengill)
Trade name for Glaucarubin

GLAUBER'S SALT
Synonym for Sodium Sulfate

GLAUCARUBIN
Trade name Glarubin (Massengill)
Administration Oral
Dosage form Tablet, 50 mg

GLOBULIN INSULIN WITH ZINC
Synonym for Globulin Zinc Insulin

GLOBULIN ZINC INSULIN
Synonym Globulin Insulin with Zinc
Administration Subcutaneous
Dosage form Vials, 40 and 80 units per

GLUCOPHYLLINE (Abbott)
Trade name for Theophylline Methylgl

FLUOROHYDROCORTISONE ACETATE
Synonym for Fludrocortisone Acetate

FLUOROMETHOLONE
Trade name Oxylone
Administration Topical
Dosage form Cream 0 025%

FLUOTHANE (Ayerst)
Trade name for Halothane

FLUOXYMESTERONE
Trade names Halotestin (Upjohn) Ultandren (Ciba)
Administration Oral
Dosage forms Tablets 2 and 5 mg

FLUPHENAZINE DIHYDROCHLORIDE
Trade names Permitil (White) Prolixin (Squibb)
Administration Oral
Dosage form Tablets 0 25 1 2 5, and 5 mg

FOLATE SODIUM
Trade name Folvite Sodium (Lederle)
Administration Parenteral
Dosage form Vial 15 mg per ml

FOLIC ACID
Trade name Folvite (Lederle)
Administration Oral intramuscular
Dosage forms Tablets, 5 10 and 20 mg ampule 15 mg per ml

FOLLUTEIN (Squibb)
Trade name for Chorionic Gonadotropin

FOLVITE (Lederle)
Trade name for Folic Acid

FOLVITE SODIUM (Lederle)
Trade name for Folate Sodium

FORTHANE (Lilly)
Trade name for Methylhexamine

FOSTEX CREAM SHAMPOO (Fostex)
Antifungal medicated shampoo

FOWLER S SOLUTION
Synonym for Potassium Arsenite Solution

FOXALIN (Grant)
Trade name for Digitoxin

FRENQUEL (Merrell)
Trade name for Azacyclonol HCl

FRUCTOSE
Synonym Levulose
Trade name Levugen (Mead Johnson)
Administration Intravenous
Dosage form Ampules, 10%

FUADIN (Winthrop)
Trade name for Stibophen

FUGILLIN (Upjohn)
Trade name for Fumagillin

FULVICIN (Schering)
Trade name for Griseofulvin

FUMAGILLIN
Trade names Fumidil (Abbott) Fugillin (Upjohn)
Administration Oral
Dosage form Tablet 10 mg

FUMERON (Standex)
Trade name for Ferrous Fumarate

FUMIDIL (Abbott)
Trade name for Fumagillin

FUNGACETIN (Harvey)
Trade name for Triacetin

FUNGIZONE (Squibb)
Trade name for Amphotericin B

FURADANTIN (Eaton)
Trade name for Nitrofurantoin

FURALTADONE
Trade name Altafur (Eaton)
Administration Oral
Dosage form Tablets, 50 and 250 mg

FURASPOR (Eaton)
Trade name for Nitrofurfuryl Methyl Ether

FURAZOLIDONE
Trade names Furoxone (Eaton), Tricofuron (Eaton)
Administration Intravaginal oral
Dosage forms Powder 0 1% suppository 0 25% tablet 100 mg solution 10 mg per ml

FURMETHIDE I (Smith, Kline & French)
Trade name for Furtrethonium I

FUROXONE (Eaton)
Trade name with Furazolidine

FURTRETHONIUM I
Trade name Furmethide I (Smith Kline & French)
Administration Subcutaneous, oral
Dosage forms Tablet 10 mg ampule, 5 mg per ml

GALACTOSE
Administration Oral
Dosage form As such

GUANIDINE HCl
Administration Oral
Dosage form Tablet, 125 mg

GYNERGEN (Sandoz)
Trade name for Ergotamine Tartrate

HALAZONE
Administration Topical
Dosage form Tablet, 4 mg to be dissolved

HALIVER OIL
Mixture of Vitamins A and D

HALOTESTIN (Upjohn)
Trade name for Fluoxymesterone

HALOTHANE
Trade name Fluothane (Ayerst)
Administration Inhalation
Dosage form Volatile liquid as such

HARMONYL (Abbott)
Trade name for Deserpidine

HARTMAN S SOLUTION
Synonym for Lactated Ringer s Solution

HEART MUSCLE EXTRACT
Trade name Cardiomone (Endo), Myocardone (Chemico)

HEDULIN (Walker)
Trade name for Phenindione

HEMO PAK (Johnson & Johnson)
Trade name for Cellulose Oxidized

HEPARIN POTASSIUM
Trade name Clarin (Leeming)
Administration Sublingual
Dosage form Tablet, 50 mg

HEPARIN SODIUM
Trade names Depo-Heparin (Upjohn), Liquaemin Sodium (Organon), Panheprin (Abbott)
Administration Subcutaneous intravenous
Dosage form Vials, 10, 50 100, 200 mg per ml

HEPTABARBITAL
Trade name Medomin (Geigy)
Administration Oral
Dosage form Tablets, 50 and 100 mg

HEPTOBEE (Endo)
Trade name for Vitamin B Complex

HEROIN
Synonym for Diacetylmorphine
Not legally available in this country for any purpose

HESPERIDIN METHYL CHALCONE
Synonym Vitamin P
Trade name Pev Gram (Ingram)
Administration Oral
Dosage form Capsule, 50 mg

HETRAZAN (Lederle)
Trade name for Diethylcarbamazine

HEXA BETALIN (Lilly)
Trade name for Pyridoxine HCl

HEXACHLOROPHENE
Trade names Gamophen (Ethicon), Hex O San (Retort), pHisoHex (Winthrop), Surgi Cen (Central)
Dosage forms Usually in soap and other preparations, 0 5 to 3 0%

HEXADIMETHRINE Br
Trade name Polybrene (Abbott)
Administration Intravenous
Dosage form Ampule, 10 mg in 10 ml

HEXAFLUORODIETHYL ETHER
Synonym Indokon
Not available on commercial drug market

HEXAMETHONIUM Br
Trade name Bistrium Br (Squibb)
Administration Subcutaneous intramuscular intravenous
Dosage form Vial 25 mg per ml

HEXAMETHONIUM Cl
Trade names Bistrium Cl (Squibb), Esomid Cl (Ciba), Hexameton Cl (Burroughs Wellcome), Methium Cl (Warner Chilcott)
Administration Oral, subcutaneous, intramuscular, intravenous
Dosage forms Tablet, 0 25 Gm vials 25 and 100 mg per ml

HEXAMETON Cl (Burroughs Wellcome)
Trade name for Hexamethonium Cl

HEXAVIBEX (Parke Davis)
Trade name for Pyridoxine HCl

HEXESTROL
Administration Oral, intramuscular
Dosage forms Tablets 1 and 3 0 mg, vials, 1 and 5 mg per ml

HEXETIDINE
Trade name Sterisil (Warner Chilcott)
Administration Intravaginal
Dosage form Gel, 0 1%

HEXOBARBITAL
Trade name Evipal (Winthrop)
Administration Oral
Dosage form Tablet, 250 mg

GLUCOSAMINE
Trade name Cosa (Pfizer)
Used with antibiotics

GLUCOSE
Synonym Dextrose
Administration Intravenous
Dosage forms Ampules containing 5 10 20 and 50% solutions

GLUCOSULFONE SODIUM
Trade name Promin (Parke Davis)
Administration Intravenous
Dosage form Ampule 0 4 Gm per ml

GLUCURONE (Reed & Carnrick)
Trade name for Glucuronolactone

GLUCURONOLACTONE
Trade name Glucurone (Reed & Carnrick)
Administration Oral
Dosage form Tablet 0 5 Gm

GLUSATE (United Labs)
Trade name for Glutamic Acid

GLUSIDE
Synonym for Saccharin

GLUTAMIC ACID
Trade name Glusate (United Labs)
Administration Oral
Dosage form Tablets 0 3 and 0 5 Gm

GLUTAMIC ACID HCl
Trade names Acidoride (Abbott) Acidothyn (Flint Eaton), Acidulin (Lilly) Aclor (Cole), Gastuloric (Warren Teed) Glutan HCl (Lederle) Hydronic (Upjohn) Muriamic (Pitman Moore)
Administration Oral
Dosage form Capsule 0 3 Gm

GLUTAN HCl (Lederle)
Trade name for Glutamic Acid HCl

GLUTAVENE (Gray)
Trade name for Sodium Glutamate

GLUTETHIMIDE
Trade name Doriden (Ciba)
Administration Tablets 125 250 500 mg

GLYCERYL GUAIACOLATE
Trade name Robitussin (Robins)
Administration Oral
Dosage form Syrup 20 mg per ml
Remarks Available only as a mixture with 0 2 mg Desoxyephedrine HCl per ml

GLYCERYL TRIACETATE
Synonym for Triacetin

GYLCERYL TRINITRATE
Synonym Nitroglycerin
Trade name Nitroglyn (Key)
Administration Sublingual
Dosage forms Tablets various sizes

GLYCINE
Synonym for Aminoacetic Acid

GLYCOBIARSOL
Trade names Amoebicon (C M C) Broxolin (Breon) Milibis (Winthrop)
Administration Topical intravaginal
Dosage forms Tablet 0 5 Gm suppository 0 25 Gm

GLYSENNID (Sandoz)
Trade name for Sennosides A and B

GLYTHEONATE (Patch)
Trade name for Theophylline Sodium Glycinate

GOLD SODIUM THIOMALATE
Trade name Myochrysine (Merck)
Administration Intramuscular
Dosage form Ampules 10 25 50 and 100 mg

GOLD SODIUM THIOSULFATE
Synonym Sodium Aurothiosulfate
Administration Intravenous intramuscular
Dosage form Ampules 10 25 50 and 100 mg

GONADOGEN (Upjohn)
Trade name for Equine Gonadotropin

GONADOTRONE (Miller)
Trade name for Pituitary Gonadotropin

GRAMICIDIN
Trade name Gramoderm (Schering)
Administration Topical
Dosage form Ointment 0 25 mg per Gm

GRAMODERM (Schering)
Trade name of Gramicidin

GRIFULVIN (McNeil)
Trade name for Griseofulvin

GRISEOFULVIN
Trade names Fulvicin (Schering) Grifulvin (McNeil)
Administration Oral
Dosage form Tablet 250 mg

GROWTH HORMONE
Synonym for Chorionic Gonadotropin

GUANATOL HCl (Lilly)
Trade name for Chloroguanide HCl

HYDRALAZINE HCl
Trade name Apresoline (Ciba)
Administration Oral, intramuscular, intravenous
Dosage forms Tablets, 10, 25, 50, 100 mg, ampule, 20 mg per ml

HYDRIODIC ACID
Administration Oral
Dosage form Syrup

HYDRIONIC (Upjohn)
Trade name for Glutamic Acid HCl

HYDROCHLORIC ACID
Administration Oral
Dosage form Diluted, 10% of free acid

HYDROCHLOROTHIAZIDE
Trade names Esidrix (Ciba), HydroDiuril (Merck), Oretic (Abbott)
Administration Oral
Dosage form Tablets, 25 and 50 mg

HYDROCORTAMATE HCl
Trade name Magnacort (Pfizer)
Administration Topical
Dosage form Ointment, 0 5%

HYDROCORTISONE
Synonym Compound F
Trade names Cort-Dome (Dome), Cortef (Upjohn), Cortril (Pfizer), Hydrocortone (Merck), Otosone-F (Broemmel)
Administration Oral, topical, intravenous
Dosage forms Tablets 5, 10 and 25 mg, ampule, 5 mg per ml, various ointments and topical lotions

HYDROCORTISONE ACETATE
Trade names Cortef Acetate (Upjohn), Cortril Acetate (Pfizer), Hydrocortone Acetate (Merck), Isopto Hydrocortisone (Alcon Labs)
Administration Oral, topical, intra articular
Dosage forms Tablet, 10 mg, ointments, 0 5, 1 0, 2 5% vial, 25 mg per ml

HYDROCORTISONE SUCCINATE
Trade name Solu Cortef (Upjohn)
Administration Intravenous
Dosage form Vial, 100 mg

HYDROCORTONE (Merck)
Trade name for Hydrocortisone

HYDROCORTONE ACETATE (Merck)
Trade name for Hydrocortisone Acetate

HYDRODIURIL (Merck)
Trade name for Hydrochlorothiazide

HYDROFLUMETHIAZIDE
Trade name Saluron (Bristol)
Administration Oral
Dosage form Tablet, 50 mg

HYDROGEN PEROXIDE
Administration Topical
Dosage form Solution, 3%

HYDROLOSE (Upjohn)
Trade name for Methylcellulose

HYDROUS WOOL FAT
Synonym Lanolin
Trade name Lamo (Tailby Nason)
Administration Topical
Dosage forms As such and in ointments

HYDROXYAMPHETAMINE HBr
Trade name Paredrine HBr (Smith, Kline & French)
Administration Oral, topical
Dosage forms Tablet, 20 mg ; solution, 1%

HYDROXYCHLOROQUINE SO_4
Trade name Plaquenil SO_4 (Winthrop)
Administration Oral
Dosage form Tablet, 200 mg

HYDROXY-DIIODOBENZYL-CYCLOHEXANE CARBOXYLIC ACID
Trade name Monophen (Bell Craig)
Administration Oral
Dosage form Capsule, 0 5 Gm

HYDROXYDIONE
Trade name Viadril (Pfizer)
Administration Intravenous
Dosage form Ampule, 1 Gm

HYDROXYMERCURI O NITROPHENOLATE
Trade name Mercurophen (Merck)
Administration Topical
Dosage form As such

HYDROXYPROGESTERONE ACETATE
Trade name Prodox (Upjohn)
Administration Oral
Dosage form Tablets, 25, 50 mg

HYDROXYSTILBAMIDINE ISETHIONATE
Administration Parenteral
Dosage form Powder, 125 mg

HYDROXYZINE HCl
Trade names Atarax (Roerig), Vistaril (Pfizer)
Administration Oral
Dosage form Tablets, 10 and 25 mg

HEXOBARBITAL SODIUM
Trade names Evipal Sodium (Winthrop) Somnalert (Warren Teed)
Administration Intravenous
Dosage form Ampules 1 and 5 Gm

HEXOCYCLIUM METHYLSULFATE
Trade name Tral (Abbott)
Administration Oral
Dosage form Tablet, 25 mg

HEX O SAN (Retort)
Trade name for Hexachlorophene

HEX O SAN SURGICAL SOAP (Retort)
Hexachlorophene soap

HEXYLCAINE HCl
Trade name Cyclaine (Merck)
Administration Topical, local
Dosage forms Topical 5% infiltration, 2%

HEXYLRESORCINOL
Trade names Caprokol (Merck) Crystoids (Merck)
Administration Oral
Dosage forms Capsule, 0 15 Gm in olive oil pills 0 1 0 2 Gm

HIBICON (Lederle)
Trade name for Benzchlorpropamide

HIPPURAN (Mallinckrodt)
Trade name for Iodohippurate Sodium

HISPRIL (Smith Kline & French)
Trade name for D phenylpyraline HCl

HISTADYL (Lilly)
Trade name for Methapyrilene HCl

HISTALOG (Lilly)
Trade name for Betazole HCl

HISTAMINASE
Trade name Torantil (Winthrop)
Administration Oral
Dosage form Tablets 10 and 20 units

HISTAMINE PO₄
Administration Subcutaneous
Dosage forms Available in tablets and ampules usually from 0 5 to 2 mg

HISTAN (Sherman)
Trade name for Pyrilamine Maleate

HISTIONEX (Strasenburgh)
Trade name for Phenyltoloxamine Resin Complex

HN₂
Common designation for Mechlorethamine

HOLOCAINE HCl
Synonym for Phenacaine HCl

HOMATROPINE METHYLBROMIDE
Trade names Mesopin (Endo), Novatrin (Campbell)
Administration Oral, subcutaneous, intramuscular
Dosage forms Tablets 2 5 and 5 0 mg ampule, 5 mg per ml

HORMESTERAL (Miller)
Trade name for Estrogenic Substances Conjugated

HUMORSOL (Merck)
Trade name for Demecarium Br

HYALURONIDASE
Trade names Alidase (Searle), Diffusin (Ortho) Hyazyme (Abbott) Infiltrase Armour), Wydase (Wyeth)
Administration Subcutaneous
Dosage form Ampule 150 U

HYAZYME (Abbott)
Trade name for Hyaluronidase

HYCODAN BITARTRATE (Endo)
Trade name for Dihydrocodeinone Bitartrate

HYDELTRA (Merck)
Trade name for Prednisolone

HYDELTRASOL (Merck)
Trade name for Prednisolone 21 PO₄

HYDELTRA T B A (Merck)
Trade name for Prednisolone Butylacetate

HYDERGINE (Sandoz)
Trade name for D hydroergocornine, Dihydroergocristine Dihydroergokryptine Mixture

HYDRABAMINE PENICILLIN G
Trade name Compocillin (Abbott)
Administration Oral
Dosage form Suspension, 60,000 units per ml.

HYDRABAMINE PENICILLIN V
Synonym for Hydrabamine Phenoxymethyl Penicillin

HYDRABAMINE PHENOXYMETHYL PENICILLIN
Synonym Hydrabamine Penicillin V
Trade name Compocillin V (Abbott)
Administration Oral
Dosage forms Tablets, 125 and 250 mg suspension, 35 mg per ml

INSOLUBLE LIVER FRACTION
Synonym for *Liver Fraction 2*

INSULIN
Trade name Iletin (Lilly)
Administration Subcutaneous
Dosage form Vials, 40, 80, 100 units per ml

INTOCOSTRIN (Squibb)
Trade name for *Chondodendron tomentosum*

INTRACAINE HCl (Philadelphia Ampule)
Trade name for Diethoxyn

INTRAHEPTOL (Lederle)
Trade name for Liver Concentrate

INTRINASE (Upjohn)
Trade name for Intrinsic Factor with Vitamin B_{12}

INTRINSIC FACTOR
Available on commercial drug market only in combination with Vitamin B_{12}

INTRINSIC FACTOR WITH VITAMIN B_{12}
Trade names Bevidoral (Abbott), Bevitab (Chicago), Bifacton (Organon), Biopar (Armour) Biopar Forte (Armour), Intrinase (Upjohn)
Administration Oral
Dosage form Tablets, of varying potency, ranging about 0 5 unit Intrinsic Factor and 25 mcg Vitamin B_{12}

INVERSINE (Merck)
Trade name for *Mecamylamine*

IODEIKON (Mallinckrodt)
Trade name for Iodophthalein Sodium

IODINATED GLYCEROL
Trade name Organidin (Wampole)
Administration Oral
Dosage forms Solution, 25 mg Iodine per ml tablet, 15 mg Iodine

IODINE
Administration Topical
Dosage forms Various concentrations and physical forms are available

IODIPAMIDE METHYLGLUCAMINE
Trade name Cholografin Methylglucamine (Squibb)
Administration Intravenous
Dosage form Ampule, 40%

IODIZED OIL
Trade name Lipiodol (Foug
Administration Instillation
Dosage form Ampules, 10
iodine

IODOALPHIONIC ACID
Trade name Priodax (Scher
Administration Oral
Dosage form Tablet, 0 5 Gm

IODO BISMUTHATE OF Q
Administration Intramuscula
Dosage form Ampule, 50 mg

IODOBRASSID
Trade name Lipoiodine (Cib
Administration Oral
Dosage form Tablet, 0 3 Gm

IODOCHLORHYDROXYQU
Trade names Vioform (Ciba
form (Ciba)
Administration Oral, intrava
Dosage forms Tablet, 0 25 Gr
0 25 Gm , powder, 25%

IODOCHLOROL (Searle)
Trade name for Chloriodized

[illegible]

ml

IODOPANOIC ACID
Synonym for Iopanoic Acid

IODOPHTHALEIN SODIUM
Synonyms Tetraiodophenolph
um, and many others
Trade names Iodeikon (Mallin
phen (Picker), Stipolac (Bu
come)
Administration Oral, intraveno
Dosage form As such

IODOPYRACET
Trade name Diodrast (Winthr
Administration Intravenous, re
Dosage form Solutions, 35 and

IONAMIN (Strasenburgh)
Trade name for *Phenyl Ter*
Resin

HYDROXYZINE PAMOATE
Trade name Vistaril (Pfizer)
Administration Oral parenteral
Dosage forms Capsules, 25, 50, 100 mg vials, 25 mg per ml

HYFLAVIN (Endo)
Trade name for Riboflavin Methylol

HYKINONE (Abbott)
Trade name for Menadione Sodium Bisulfite

HYMORPHAN HCl (Endo)
Trade name for Dihydromorphinone HCl

HYOSCINE
Synonym for Scopolamine

HYOSCINE HBr
Synonym for Scopolamine HBr

HYOSCINE METHYLBROMIDE
Synonym for Methscopolamine HBr

l HYOSCYAMINE HBr
Administration Oral
Dosage forms Tablets of various sizes

HYPAQUE SODIUM (Winthrop)
Trade name for Diatrizoate Sodium

HYPO
Synonym for Sodium Thiosulfate

HYTAKEROL (Winthrop)
Trade name for Dihydrotachysterol

I^{131}
Synonym for Sodium Radio-Iodide

I^{132}
Synonym for Radio Iodine^{132}

I^{133}
Synonym for Radio Iodine^{133}

ICHTHALBIN (Bilhuber Knoll)
Trade name for Ichthyol Albuminate

ICHTHAMMOL
Administration Topical
Dosage forms Various 5 to 20%

ICHTHYOL ALBUMINATE
Trade name Ichthalbin (Bilhuber Knoll)
Administration Oral, topical
Dosage form Tablet 0 3 Gm

ILETIN (Lilly)
Trade name for Insulin

ILIDAR (Roche)
Trade name for Azapetine PO_4

ILOPAN (Warren Teed)
Trade name for Pantothenyl Alcohol

ILOSONE (Lilly)
Trade name for Erythromycin Propionate

ILOTYCIN (Lilly)
Trade name for Erythromycin

IMFERON (Lakeside)
Trade name for Iron Dextran

IMIDAZOLE
Trade name Carbinazole (Denver)
Not available on commercial drug market

IMIPRAMINE HCl
Trade name Tofranil (Geigy)
Administration Oral, intramuscular
Dosage forms Tablet, 25 mg ampule 12 5 mg per ml

INDIGO CARMINE
Synonym for Sodium Indigotindisulfonate

INDOKON
Synonym for Hexafluorodiethyl Ether

INDON (Parke, Davis)
Trade name for Phenindione

INESTRA (Merck)
Trade name for Ethinyl Estradiol

INFILTRASE (Armour)
Trade name for Hyaluronidase

INFUNDIN (Burroughs Wellcome)
Trade name for Pituitary Extract (Posterior)

INH (Lilly)
Trade name for Isoniazid

INHISTON (Union)
Trade name for Pheniramine Maleate

INOSITOL
Administration Oral
Dosage forms Tablet and capsule 0 5 Gm

INOSITOL HEXANITRATE
Trade name Tolanate (C S C)
Administration Oral
Dosage form Tablet, 10 mg

INOSITOL HEXAPHOSPHATE
Trade name Calciphos (Bilhuber Knoll)
Administration Oral
Dosage form Tablet, 0 4 Gm.

ISONIAZID
Synonym Isonicotinic Acid Hydrazide
Trade names Armazide (Armour), Cotinazin (Pfizer), Dinacrin (Winthrop), Ditubin (Schering), INH (Lilly), Isolyn (Abbott), Niadrin (Endo), Niconyl (Parke Davis), Nicozide (Premo), Nydrazid (Squibb), Pyricidin (Nepera), Rimifon (Roche), Tisin (Arlington) Tyvid (Merrell), and others
Administration Oral intramuscular
Dosage forms Various forms

ISONICOTINIC ACID HYDRAZIDE
Synonym for Isoniazid

ISONIPECAINE
Synonym for Meperidine

ISONORIN SO₄ (C. D Smith)
Trade name for Isoproterenol SO

ISO PAR (Medical Chem)
Trade name for Coparaffinate

ISOPHANE INSULIN
Synonym NPH Insulin
Trade name NPH Iletin (Lilly)
Administration Subcutaneous
Dosage forms Various concentrations

ISOPROPAMIDE I
Trade name Darbid (Smith Kline & French)
Administration Oral
Dosage form Tablet, 5 mg

ISOPROPYL ALCOHOL
Administration Topical
Dosage form Solutions 70 to 80%

ISOPROTERENOL HCl
[illegible]
Administration Sublingual inhalation
Dosage forms Tablet, 5, 10, 15 mg , solution 1 100, 1 200

ISOPROTERENOL SO₄
Trade names Isonorin SO₄ (Smith, Carroll, Dunham), Norisodrine SO₄ (Abbott)
Administration Inhalation sublingual
Dosage forms Powder, 25%, solution, 1% tablet, 10 mg

ISOPTO CORTISONE (Alcon)
Trade name for Cortisone Acetate

ISOPTO HYDROCORTISONE (Alcon)
Trade name for Hydrocortisone Acetate

ISORDIL (Ives)
Trade name for Isosorbide Dinitrate

ISOSORBIDE DINITRATE
Trade name Isordil (Ives)
Administration Oral
Dosage form Tablet, 10 mg

ISOTHIPENDYL HCl
Trade name Theruhistin (Ayerst)
Administration Oral
Dosage forms Tablet, 4 mg sustained action tablet 12 mg , syrup, 0 4 mg per ml

ISOTONIC SOLUTION OF THREE CHLORIDES
Synonym for Ringer s Solution

ISOXSUPRINE HCl
Trade name Vasodilan (Mead Johnson)
Administration Oral, intramuscular
Dosage forms Tablet, 10 mg , ampule, 5 mg per ml

ISTIZIN (Winthrop)
Trade name for Dihydroxyanthraquinone

ISUPREL HCl (Winthrop)
Trade name for Isoproterenol HCl

ITRUMIL SODIUM (Ciba)
Trade name for Iothiouracil Sodium

JALAP
Administration Oral
Dosage form As such

JUNIPER TAR
Synonym Cade Oil
Administration Topical
Dosage forms Various, 1 to 20%

KADALEX (Don Baxter)
Trade name for Potassium Cl in Dextrose

KALPIN (Wallace)
Trade name for Sodium and Calcium Alginate

KANAMYCIN SO₄
Trade name Kantrex (Bristol)
Administration Oral intramuscular
Dosage forms Capsule 0 5 Gm vials, 0 25 and 0 33 Gm per ml

KANTREX (Bristol)
Trade name for Kanamycin SO₄

KAON (Warren Teed)
Trade name for Potassium Gluconate

KAOPECTATE (Upjohn)
Trade name for a mixture of Kaolin and Pectin

IOPANOIC ACID
Synonym Iodopanoic Acid
Trade name Telapaque (Winthrop)
Administration Oral
Dosage form Tablet, 0 5 Gm

IOPHENDYLATE
Synonym Ethyl Iodophenylundecylate
Trade names Mulsopaque (Lafayette), Pantopaque (Lafayette)
Administration Parenteral
Dosage form As such, 50% emulsion

IOPHENOXIC ACID
Trade name Teridax (Schering)
Administration Oral
Dosage form Tablet, 0 75 Gm

IOTHIOURACIL SODIUM
Trade name Itrumil Sodium (Ciba)
Administration Oral
Dosage form Tablet, 50 mg

IPECAC
Administration Oral
Dosage forms As such, fluid extract, syrup

IPRAL SODIUM (Squibb)
Trade name for Probarbital Sodium

IPRONIAZID
Trade name Marsilid (Roche)
Administration Oral
Dosage form Tablets, 10, 25, 50 mg

IRON AND AMMONIUM CITRATE
Administration Oral, intramuscular
Dosage forms Capsule, 0 5 Gm , vial, 50 mg

IRON AND BILE SALTS
Trade name Bilron (Lilly)
Administration Oral
Dosage form Tablets, 0 16, 0 3 Gm

IRON CACODYLATE
Synonym for Ferric Cacodylate

IRON CARBOHYDRATE COMPLEX
Trade name Astrafer (Astra)
Administration Intravenous
Dosage form Solution, 20 mg iron per ml

IRON CHOLINE CITRATE
Synonym for Ferrocholinate

IRON HYDROXIDE, COLLOIDAL
Administration Oral
Dosage form Tablet, 75 mg

IRON OXIDES
Synonym for Ferric Oxides

IRON-DEXTRAN
Trade name Imferon (Lakeside)
Administration Intramuscular
Dosage form Ampule, 50 mg per ml

IROX (Cole)
Trade name for Ferrous Gluconate

ISOBARB (U. S. Standard)
Trade name for Pentobarbital Sodium

ISOBORNYL THIOCYANOACETATE
Trade name Bornate (Wyeth)
Administration Topical
Dosage form Emulsion, 5%

ISOCARBOXAZID
Trade name Marplan Br (Roche)
Administration Oral
Dosage form Tablets, 5 and 10 mg

ISOCRIN (Warner-Chilcott)
Trade name for *Diacetylhydroxyphenylisatin*

ISODINE (Isodine)
Trade name for Povidone-Iodine

ISOEPHEDRINE HCl
Synonym Pseudoephedrine HCl
Trade name Sudafed (Burroughs Wellcome)
Administration Oral
Dosage form Tablet, 32 mg

ISOFEDROL (Blue Line)
Trade name for Ephedrine SO_4

ISOFLUROPHATE
Synonym DFP
Trade name Floropryl (Merck)
Administration Topical
Dosage forms Solution, 0 1%, ointment, 0 025%

ISO-IODEIKON (Mallinckrodt)
Trade name for Phentetiothalein Sodium

ISOLYN (Abbott)
Trade name for Isoniazid

ISOMETH (Lloyd)
Trade name for Isometheptene Tartrate

ISOMETHEPTENE HCl
[illegible]

ISOMETHEPTENE TARTRATE
Trade name Isometh (Lloyd)
Administration Intravenous, subcutaneous
Dosage form Vial, 100 mg per ml

LANOXIN (Burroughs Wellcome)
Trade name for Digoxin

LAURON (Endo)
Trade name for Aurothioglycanide

LEAD OLEATE
Trade name Diachylon Ointment (Ulmer)
Administration Topical
Dosage form Ointment 50%

LECITHIN
Administration Oral
Dosage form As such

LEDERPLEX (Lederle)
Trade name for Vitamin B Complex

LENIGALLOL (Bilhuber Knoll)
Trade name for Acetpyrogall

LENTE ILETIN (Lilly)
Trade name for Lente Insulin

LENTE INSULIN
Trade name Lente Iletin (Lilly)
Administration Subcutaneous
Dosage form Vials 40 and 80 units per ml

LENTOPEN (Wyeth)
Trade name for Procaine Penicillin G

LERITINE HCl (Merck)
Trade name for Anileridine HCl

LERITINE PO_4 (Merck)
Trade name for Anileridine PO_4

LESCOPINE Br (Lincoln)
Trade name for Methscopolamine Br

LETHIDRONE (Burroughs Wellcome)
Trade name for Nalorphine HBr

LEUCOVORIN (Lederle)
Trade name for Citrovorum Factor

LEUKERAN (Burroughs Wellcome)
Trade name for Chlorambucil

LEVALLORPHAN TARTRATE
Trade name Lorfan (Roche)
Administration Parenteral
Dosage form Vial 1 mg per ml

LEVARTERENOL BITARTRATE
Trade name Levophed
Administration Intravenous
Dosage form Solution 1:1 000

LEVO DROMORAN TARTRATE (Roche)
Trade name for Levorphan Tartrate

LEVOHYOSCYAMINE SO_4
Trade names Levsin SO_4 (Kremers Urban) Levsinex (Kremers Urban)
Administration Oral
Dosage form Tablet 0.25 mg

LEVONOR (Nordmark)
Trade name for l-Amphetamine Alginate

LEVOPHED (Winthrop)
Trade name for Levarterenol Bitartrate

LEVO PROPOXYPHENE
Not yet available on commercial drug market

LEVORPHAN TARTRATE
Trade name Levo Dromoran Tartrate (Roche)
Administration Oral subcutaneous
Dosage forms Tablet 2 mg ampule 2 mg per ml

LEVSIN SO_4 (Kremers Urban)
Trade name for Levohyoscyamine SO_4

LEVSINEX (Kremers Urban)
Trade name for Levohyoscyamine SO_4

LEVUGEN (Mead Johnson)
Trade name for Levulose

LEVULOSE
Synonym for Fructose

LIDOCAINE HCl
Trade name Xylocaine HCl (Astra)
Administration Topical and parenteral
Dosage forms A variety of forms

LIFEBUOY SOAP (Lever)
Tetramethyl Thiuram Disulfide soap

LINAMPHETA (Lincoln)
Trade name for Amphetamine SO_4

LINIT (Corn Products)
Trade name for Starch

LIOTHYRONINE SODIUM
Synonym l-Triiodothyronine
Trade names Cytomel (Smith Kline & French) Trionine (Roche)
Administration Oral
Dosage form Tablets 5 25 and 50 mcg

LIPIODOL (Fougera)
Trade name for Iodized Oil

LIPO ADRENAL CORTEX
Administration Intramuscular
Dosage form Ampule equivalent of 1 mg Hydrocortisone per ml

KAPPADIONE (Lilly)
Trade name for Menadiol Sodium PO,

KAPPAXIN (Winthrop)
Trade name for Menad one

KAPRYLEX (Strasenburgh)
Trade name for Resin Caprylate

KATONIUM (Winthrop)
Trade name for Styronate Res ns

KAYEXALATE (Winthrop)
Trade name for Sodium Polystyrene S lfonate

KAYKLOT (Raymer)
Trade name for Menadione

KAYQUINONE (Abbott)
Trade name for Menad one

KEMADRIN (Burroughs Wellcome)
Trade name for Procycl d ne HCl

KENACORT (Squibb)
Trade name for Triamcinolone

ENALOG (Squibb)
rade name for Triamcinolone Acetonide

ERAPHEN (Picker)
rade name for Iodophthalein Sod um

FTOCHOL (Searle)
ade name for Bile Extract ves

Y SERPINE (Key)
de name for Reserp ne

ELISEM (Massengill)
le name for Visammin mater al

LLIN
nym for Visammin

GAMIN (Merrell)
name for Oxal c and Malon c Ac d ture

UCOID (Panray)
name for Alseroxylon

LOT (Cole)
ame for Menadione

CREAMS A and D (Dome)
luble Tar preparation 2%

KONAKION (Roche)
Trade name for Phytonadione

KONDREMUL (Patch)
Trade name for Petrolatum

KONOGEN (Lilly)
Trade name for Estrogen c Substances Conjugated

KONSYL (Burton Parsons)
Trade name for Plantago Concentrate

KOROTRIN (Winthrop)
Trad name for Chorion c Gonadotropin

KUTROL (Parke Davis)
Trade name for U roenterone

KWELL (Reed & Carnrick)
Trade name for Gamma Benzene Hexachlo r l

KYNEX (Lederle)
Tr de na e for Sulfamethoxypyridazine

KYNEX ACETYL (Lederle)
Trad nume for Sulfa nethoxypyridaz ne A etyl

LACHESINE
Not ava lable on the commercial drug market

LACTATED RINGER S SOLUTION
Synonym Hartman s Solut on
Administration Intravenous subcutaneous
Dosage form Ampules and bottles as such

LACTOFLAVIN
Synonym for Riboflavin

LACTOSE
Available in the form of Alpha Lactose

LA FORMULA (Burton Parsons)
Trade name for Plantago Concentrate

LANO (Tailby Nason)
Trade name for Lanol n

LANATOSIDE C
Trade name Ced lanid Sa doz
Administration Oral ntramuscular intravenous
Dosage forms Tablet 0 5 mg ampules 2 mg per ml

LANOLIN
Synonym for Hydrous Wool Fat

LUTEIN (Hynson)
Trade name for Corpus Luteum

LUTEOTROPHIN (Squibb)
Trade name for Prolactin

LUTOCYLIN (Ciba)
Trade name for Progesterone

LUTOCYLOL (Ciba)
Trade name for Ethisterone

LUTREXIN (Hynson)
Trade name for Lututrin

.UTROMONE (Endo)
Trade name for Progesterone

.UTUTRIN
Trade name Lutrexin (Hynson)
Administration Oral
Dosage form Tablet, 1,000 units

.YNORAL (Organon)
Trade name for Ethinyl Estradiol

.YOCYTE (Merck)
Trade name for Red Blood Cells, Human Dried

MAALOX (Rorer)
Trade name for Magnesium and Aluminum Hydroxide Mixture

MADRIBON (Roche)
Trade name for Sulfadimethoxine

MADRIQID (Roche)
Trade name for Sulfadimethoxine

MAFENIDE HCl
Trade name Sulfamylon HCl (Winthrop)
Administration Topical
Dosage form Solution, 5%

MAGMASIL (Leeming)
Trade name for Magnesium Trisilicate

MAGNACORT (Pfizer)
Trade name for Hydrocortamate HCl

MAGNAMYCIN (Pfizer)
Trade name for Carbomycin

MAGNEPHYLLINE (Sherman)
Trade name for Magnesium Theophylline

MAGNESIA MAGMA
Synonym for Magnesium Hydroxide

MAGNESIUM AND ALUMINUM HYDROXIDE MIXTURE
Trade names Aludrox (Wyeth), Maalox (Rorer)
Administration Oral
Dosage forms Suspension, tablet

MAGNESIUM CO_3
Administration Oral
Dosage form As such

MAGNESIUM CITRATE
Administration Oral
Dosage form Solution, 6%

MAGNESIUM GLUCONATE
Trade names Almora (Durst), Menesia (Pitman-Moore)
Administration Oral
Dosage form Tablet, 0 5 Gm

MAGNESIUM HYDROXIDE
Synonyms Magnesia Magma, Milk of Magnesia
Dosage forms As such, suspension, 7 5%, tablet, 0 3 Gm

MAGNESIUM OXIDE
Administration Oral, topical
Dosage form As such

MAGNESIUM PO_4
Administration Oral
Dosage form As such

MAGNESIUM SO_4
Synonym Epsom salts
Administration Oral
Dosage form Crystals

MAGNESIUM THEOPHYLLINE
Trade name Magnephylline (Sherman)
Administration Oral
Dosage form Tablets, 0 1 Gm

MAGNESIUM TRISILICATE
Trade names Magmasil (Leeming), Trinesium (Abbott), Tri Sil (Warren Teed)
Administration Oral
Dosage forms Tablet, 0 5 Gm, as such, suspensions of various concentrations

MAGNESIUM TRISILICATE AND ALUMINUM HYDROXIDE
Trade names Gelusil (Warner Chilcott), A M T (Wyeth), Magsal (Endo), Milk of Trinesium (Abbott), Tri Creamalate (Winthrop), Trisogel (Lilly)
Administration Oral
Dosage forms Tablet, 0 5 Gm, suspensions of various concentrations

LIPO BISMOL (Parke, Davis)
Trade name for Bismuth Octyloxyacetate

LIPO DIAZINE (Donley Evans)
Trade name for Sulfadiazine

LIPOGANTRISIN (Roche)
Trade name for Acetyl Sulfisoxazole

LIPOIODINE (Ciba)
Trade name for Iodobrassid

LIPO LUTIN (Parke Davis)
Trade name for Progesterone

LIPO TRIAZINE (Donley Evans)
Trade name for Meth Dia Mer Sulfonamides

LIQUAEMIN SODIUM (Organon)
Trade name for Heparin Sodium

LIQUAMAR (Organon)
Trade name for Phenprocoumon

LIQUIPRIN (Johnson & Johnson)
Trade name for Salicylamide

LITHIUM ANTIMONY THIOMALATE
Synonym Anthiomaline
Administration Parenteral
Dosage form Ampule, 60 mg per ml

LIVER CONCENTRATE
Trade name Intraheptol (Lederle)
Administration Intravenous
Dosage form Vial 1 ml equals 33 3 Gm liver

LIVER DESICCATED
Administration Oral
Dosage form Capsule, 0 5 Gm

LIVER EXTRACT, ORAL
Administration Oral
Dosage forms Powder, about 15 Gm per unit Liquid, 45 ml per unit

LIVER FRACTION 1
Synonym Soluble Liver Fraction

IVER FRACTION 2
ynonym Insoluble Liver Fraction
dministration Oral

IVER INJECTION, CRUDE
ade name Campolon (Winthrop)
lministration Intramuscular
sage form Ampule, 2 units per ml

LIVER INJECTION, PURIFIED
Trade names Pernaemon (Organon), R ticulogen (Lilly)
Administration Intramuscular
Dosage form Vials, equivalent of 10 and 2 mcg Vitamin B_{12} per ml

LOBELIN (Bischoff)
Trade name for Alpha Lobelin HCl

LOBELINE (Sandoz)
Trade name for Alpha Lobeline HCl

LORFAN TARTRATE (Roche)
Trade name for Levallorphan Tartrate

LORINAL (Arnar Stone)
Trade name for Chloral Hydrate

LOTIO ALBA
Synonym for White Lotion

LOTUSATE (Winthrop)
Trade name for Talbutal

LOWILA (Westwood)
Detergent cleanser

LUASMIN (Brewer)
Each capsule or tablet contains Theophylline Sodium Acetate 0 2 Gm Ephedrine SO 30 mg Phenobarbital Sodium 30 mg

LUBRIDERM (Texas Pharmacal)
Lanolin emulsion

LUCORTEUM (Merck)
Trade name for Progesterone

LUGOL S SOLUTION
Synonym for Strong Iodine Solution

LULLAMIN (Reed & Carnrick)
Trade name for Methapyrilene HCl

LUMINAL (Winthrop)
Trade name for Phenobarbital

LUMINAL SODIUM (Winthrop)
Trade name for Phenobarbital Sodium

LUNAR CAUSTIC
Synonym for Silver NO_3

LUNARGEN (Lilly)
Trade name for Silver Protein, Mild

LUNOSOL (Hille)
Trade name for Silver Cl, Colloidal

MELLARIL (Sandoz)
Trade name for Thioridazine HCl

MELONINE (Upjohn)
Trade name for Methoxsalen

MELOZETS (Merck)
Trade name for Methylcellulose

MENADIOL SODIUM PO₄
Trade names Kappadione (Lilly), Synkayvite (Roche) Thylokay (Squibb)
Administration Oral, parenteral
Dosage forms Tablet, 5 mg , ampules, 1, 2 5, 5, 10 37 5, and 75 mg per ml

MENADIONE
Synonym Vitamin K Synthetic
Trade names Kappaxin (Winthrop), Kayklot (Raymer), Kayquinone (Abbott), Kolklot (Cole)
Administration Oral, intramuscular
Dosage forms Tablets, 1, 2 mg , ampules containing 2 to 4 mg in oil

MENADIONE SODIUM BISULFITE
Trade name Hykinone (Abbott)
Administration Intramuscular
Dosage form Ampule, 4 mg per ml

MENESIA (Pitman Moore)
Trade name for Magnesium Gluconate

MENTHOL
Administration Topical
Dosage forms Various, 0 1 to 1%

MEONINE (Wyeth)
Trade name for Methionine

MEPACRINE HCl
Synonym for *Quinacrine HCl*

MEPAZINE ACETATE
Trade name Pacatal Acetate (Warner Chilcott)
Administration Intramuscular intravenous
Dosage form Vial, 25 mg per ml

MEPAZINE HCl
Synonym Pecazine
Trade name *Pacatal HCl (Warner Chilcott)*
Administration Oral, intramuscular
Dosage forms Tablets, 25, 50 mg , ampule, 25 mg per ml

MEPENZOLATE METHYLBROMIDE
Trade name Cantil (Lakeside)
Administration Oral
Dosage form Tablet, 25 mg

MEPERIDINE HCl
Synonyms Isonipecaine, Pethidine
Trade name Demerol HCl (Winthrop)
Administration Oral, subcutaneous, intramuscular, intravenous
Dosage forms Tablets, 50 100 mg , ampule, 50 mg per ml , elixir, 10 mg per ml

MEPHENESIN
Trade names Daserol (Evron), Dioloxol (Carnrick), Mepherol (Bryant), Mephson (Tutag), Myanesin (Biorganic), Myoxane (Ascher) Oranixon (Organon), Prolax (Cole), S nan (Warren Teed), Thoxidil (Normand), Tolhart (Hart), Tolosate (Brewer), Tolserol (Squibb), Tolulox (Miller), and many others
Administration Oral
Dosage forms *Tablets, 100, 250, and 500 mg*

MEPHENESIN CARBAMATE
Trade name Tolseram (Squibb)
Administration *Oral*
Dosage form Tablet, 0 5 Gm

MEPHENTERMINE SO₄
Trade name Wyamine (Wyeth)
Administration Intranasal, intravenous, intramuscular, oral
Dosage forms Inhaler, 250 mg solution 15 mg per ml tablets, 12 5 and 25 mg

MEPHEROL (Bryant)
Trade name for Mephenesin

MEPHOBARBITAL
Trade name Mebaral (Winthrop)
Administration Oral
Dosage form *Tablets, 30, 50, 100, and 200 mg*

MEPHSON (Tutag)
Trade name for Mephenesin

MEPHYTON (Merck)
Trade name for Phytonadione

MEPIPERPHENIDOL Br
Trade name *Darstine Br (Merck)*
Administration Oral
Dosage form Tablets, 50 and 100 mg

MEPRANE DIPROPIONATE (Reed & Carnrick)
Trade name for Promesthestrol Dipropionate

MEPROBAMATE
Trade names Equanil (Wyeth) Meprospan (Wallace), Miltown (Wallace)
Administration Oral
Dosage forms Tablet and capsule, 200 and 400 mg

MAGSAL (Endo)
Trade name for Magnesium Trisilicate and Aluminum Hydroxide

MALESTRONE (Kirk)
Trade name for Testosterone

MALLOPHENE (Mallinckrodt)
Trade name for Phenylazo-diamino pyridine HCl

MANADRIN (Endo)
Trade name for Ephedrine

MANDELAMINE (Nepera)
Trade name for Methenamine Mandelate

MANDELIC ACID
Administration Oral
Dosage form As such

MANICOLE (Cole)
Trade name for Mannitol Hexanitrate

MANNITOL
Administration Intravenous
Dosage form Ampule 25%

MANNITOL HEXANITRATE
Trade names Manicole (Cole) Maxitate (Strasenburgh) Nitranitol (Merrell)
Administration Oral
Dosage form Tablet 30 mg

MANVENE (Searle)
Trade name for Mytatrienediol

MAPHARSEN (Parke Davis)
Trade name for Oxophenarsine HCl

MARCUMAR (Roche)
Trade name for Phenprocoumon

MAREZINE (Burroughs Wellcome)
Trade name for Cyclizine

MAREZINE HCl (Burroughs Wellcome)
Trade name for Cyclizine HCl

MAREZINE LACTATE (Burroughs Wellcome)
Trade name for Cyclizine Lactate

MARPLAN Br (Roche)
Trade name for Isocarboxazid

MARSILID (Roche)
Trade name for Iproniazid

MASENATE (Schieffelin)
Trade name for Testosterone Propionate

MASENONE (Schieffelin)
Trade name for Methyltestosterone

MATROMYCIN (Pfizer)
Trade name for Oleandomycin PO_4

MAXITATE (Strasenburgh)
Trade name for Mannitol Hexanitrate

MAXUKAL (Breon)
Trade name for Calcium Kinate Gluconate

MAZON (Belmont)
Coal tar soap

MEBARAL (Winthrop)
Trade name for Mephobarbital

MECAMYLAMINE
Trade name Inversine (Merck)
Administration Oral
Dosage form Tablets 2.5 and 10 mg

MECHLORETHAMINE HCl
Synonym HN_2
Trade names Mustargen HCl (Merck) Caryolysine HCl (Merck)
Administration Intravenous
Dosage form Vial 10 mg

MECHOLYL Br (Merck)
Trade name for Methacholine Br

MECHOLYL Cl (Merck)
Trade name for Methacholine Cl

MECLIZINE HCl
Synonym Postafene
Trade names Bonamine (Pfizer) Bonine (Pfizer)
Administration Oral
Dosage form Tablet 25 mg

MECOSTRIN Cl (Squibb)
Trade name for Dimethyl Tubocurarine Cl

MEDIHALER NITRO (Riker)
Trade name for Octyl Nitrite

MEDINAL (Warner Chilcott)
Trade name for Barbital Sodium

MEDOMIN (Geigy)
Trade name for Heptabarbital

MEDROL (Upjohn)
Trade name for Methylprednisolone

MEGIMIDE (Abbott)
Trade name for Bemegride

MELAMINE
Synonym for Triethylene Melamine

MERTESTATE (Breon)
Trade name for Testosterone

MERTHIOLATE (*Lilly*)
Trade name for Thimerosal

MERTHYLLINE (Drug Products)
Trade name for Mercurophylline

MERYTHROL (Chemico)
Trade name for Salicylophenylformic Acid

MESANTOIN (Sandoz)
Trade name for Methylphenylethylhydantoin

MESOPIN (Endo)
Trade name for Homatropine Methylbromide

MESTILBOL
Trade name Monomestrol (Wallace & Tiernan)
Administration Oral, intramuscular
Dosage forms Tablets, 0 25, 0 5, 1, 2 5 mg , ampules, 10, 25 mg in 1 ml of oil

MESTINON Br (Roche)
Trade name for Pyridostigmin Br

METACRESYL ACETATE
Trade name Cresatin (Merck)
Administration Topical
Dosage form Ointment, 80%

METADEE (Merck)
Trade name for Calciferol

METAMINE (Leeming)
Trade name for Aminotrate

METAMUCIL (Searle)
Trade name for Psyllium

METANDREN (*Ciba*)
Trade name for Methyltestosterone

METAPHEN (Abbott)
Trade name for Nitromersol

METARAMINOL BITARTRATE
Trade name Aramine Bitartrate (Merck)
Administration Intranasal, intravenous, intramuscular
Dosage form Solutions, 0 25 and 1 0%

METHACHOLINE Br
Trade name Mecholyl Br (Merck)
Administration Oral
Dosage form Tablet, 0 2 Gm

METHACHOLINE Cl
Trade name Mecholyl Cl (Merck)
Administration Oral, subcutaneous, ion transfer
Dosage forms Powder, ampule, 25 mg

METHADONE HCl
Synonym Amidone HCl
Trade names Adanon HCl (Winthrop), Althose (Wyeth), Dolophine HCl (Lilly)
Administration Oral, subcutaneous, intravenous
Dosage forms 2 5, 5 0, 7 5, and 10 mg , ampules, 5 and 10 mg per ml

METHADRINE HCl (Burroughs Wellcome)
Trade name for Methamphetamine HCl

METHAFURYLENE FUMARATE
Trade name Foramalin (Eaton)
Administration Oral
Dosage form Tablet, 50 mg

METHALLATAL
Trade name Mosidal (Abbott)
Administration Oral
Dosage form Tablet, 150 mg

METHALLENESTRIL
Trade name Vallestril (Searle)
Administration Oral
Dosage form Tablet, 3 mg

METHA-MERDIAZINE (*McNeil*)
Trade name for Meth Dia Mer-Sulfonamides

METHAMOCTOL
Trade name Aranthol (Bilhuber Knoll)
Administration Oral, intravenous
Dosage forms Tablet, 130 mg , ampule, 100 mg per ml

[illegible]

METHAMPHIN (Rorer)
Trade name for Methamphetamine *HCl*

METHAMPYRONE (Testagar)
Trade name for Dipyrone

METHANDRIOL
Synonyms Diolostene, Methylandrostenediol
Trade names Androdiol (Carnrick), Diolandrone (Carnrick), Drostene (Ascher), Methostan (*Schering*), Nabadial (Breon), Neostene (Miller), Stenediol (Organon)
Administration Oral, intramuscular, sublingual, buccal
Dosage forms Tablets, 10 and 25 mg , vials, 25 and 50 mg per ml

MEPROSPAN (Wallace)
Trade name (long acting) for Meprobamate

MERATRAN (Merrell)
Trade name for Pipradrol HCl

MERBAK (Schieffelin)
Trade name for Acetomeroctol

MERBROMIN
Trade name Mercurochrome (Hynson)
Dosage forms As such tablet, 0 3 Gm so lution 2%

MERCAPTOMERIN
Trade name Diucardyn (Ayerst) Thiomerin (Wyeth)
Administration Subcutaneous intramuscular
Dosage form Vials 10 and 30 ml

MERCAPTOPURINE
Trade name Purinethol (Burroughs Well come)
Administration Oral
Dosage form Tablet 50 mg

MERCOCRESOLS
Trade name Mercresin (Upjohn)
Administration Topical
Dosage form Tincture 0 2%

MERCODINONE (Merrell)
Trade name for Dihydrocodeinone Bitartrate

MERCRESIN (Upjohn)
Trade name for Mercocresols

MERCUMATILIN
Trade name Cumertilin (Endo)
Administration Oral intramuscular
Dosage forms Tablets vials 1 2 10 ml

MERCUPURIN (Campbell)
Original trade name for Mercurophylline

MERCURASCORB (Funk)
Trade name for mixture of Mercurophylline and Ascorbic Acid

MERCURIAL OINTMENT MILD
Synonym Blue Ointment
Administration Topical
Dosage form Ointment 10%

MERCURIC Cl
Synonyms Corrosive Sublimate Bichloride of Mercury
Dosage form As such

MERCURIC OXIDE, RED
Administration Topical
Dosage form Ointment, 5 to 10%

MERCURIC OXIDE, YELLOW
Administration Topical
Dosage form Ointment, 1%

MERCURITAL
Not available on commercial drug market

MERCUROCHROME (Hynson)
Trade name for Merbromin

MERCUROPHEN (Merck)
Trade name for Hydroxymercuri-o-nitrophen olate

MERCUROPHYLLIN D U *(Kremers Ur ban)*
Trade name for Mercurophylline

MERCUROPHYLLINE
Trade names Diumerin (C D Smith) Mercurascorb (Funk) Mercupurin (Camp bell) Mercurophyllin D U (Kremers Ur ban) Mercuzanthin (Campbell), Merthyl line (Drug Products)
Administration Oral intramuscular
Dosage forms Tablet, 74 mg vial, 2 ml

MERCUROUS Cl
Synonym for Mild Mercurous Cl

MERCUZANTHIN (Campbell)
Trade name for Mercurophylline

MER DIAZINE (McNeil)
Trade name for Dia Mer Sulfonamides

MERETHOXYLLINE PROCAINE
Trade name *Dicurin Procaine (Lilly)*
Administration Intramuscular
Dosage form Vials 2 and 10 ml

MERGAMATE
Not available on commercial drug market

MERPHENYL BORATE (Hamilton)
Trade name for Phenylmercuric Borate

MERPHENYL NO₃ (Hamilton)
Trade name for Phenylmercuric NO_3

MERPURATE
Not available on commercial drug market

MERSALYL AND THEOPHYLLINE
Trade names Mersalyn (Kirk) Salyrgan theophylline (Winthrop) Theomersyl which contains the sodium glycinate of theophylline (Central)
Administration Intramuscular
Dosage form Vial, 2 ml

MERSALYN (Kirk)
Trade name for Mersalyl and Theophylline

METHOXYLENE (McNeil)
Trade name for Methapyrilene HCl

METHOXYPHENAMINE HCl
Trade name Orthoxine HCl (Upjohn)
Administration Oral
Dosage form Tablet 100 mg

METHOXYPROMAZINE MALEATE
Trade name Tentone (Lederle)
Administration Oral
Dosage forms Tablets, 10, 25, 50 mg

METHSCOPOLAMINE Br
Synonyms Hyoscine Methylbromide, Scopolamine Methylbromide, Epoxymethamine Br
Trade names Lescopine Br (Lincoln), Pamine (Upjohn), Proscomide (Miller)
Administration Oral
Dosage forms Tablet, 2 5 mg capsule, 7 5 mg

METHSCOPOLAMINE NO_3
Trade name Skopolate (Strasenburgh)
Administration Oral, subcutaneous, intramuscular
Dosage forms Tablet, 2 mg ampule, 2 mg per ml

METHSUXIMIDE
Trade name Celontin (Parke, Davis)
Administration Oral
Dosage form Capsule, 0 3 Gm

METHYLAMINOHEPTANE HCl
Trade name Oenethyl HCl
Administration Intravenous
Dosage form Solution 50 mg per ml

METHYLANDROSTENEDIOL
Synonym for Methandriol

METHYL ATROPINE NO_3
Trade name Metropine (Strasenburgh)
Administration Oral subcutaneous, intramuscular
Dosage forms Tablet, 1 mg, elixir, 0 25 mg per ml ampule, 2 mg per ml

METHYLCELLULOSE
Trade names Cellothyl (Warner Chilcott), Cologel (Lilly), Hydrolose (Upjohn), Melozets (Merck), Methylose (Rowell), Premocel (Premo) Syncelose (Blue Line)
Administration Oral
Dosage forms Various forms

METHYL CYCLOHEXENYL METHYL-BARBITURIC ACID
Trade name Sombulex (Schenley)
Administration Oral
Dosage form Tablet, 0 25 Gm

METHYLENE BLUE
Administration Intravenous
Dosage form Vial, 60 ml 2% solution

METHYLERGONOVINE TARTRATE
Trade name Methergine Tartrate (Sandoz)
Administration Oral, intravenous, intramuscular
Dosage forms Ampule, 0 2 mg per ml fluid, 0 25 mg per ml, tablet, 0 25 mg

METHYLGLUCAMINE DIATRIZOATE
Trade names Cardiografin (Squibb), Gastrografin (Squibb), Renografin (Squibb)
Remarks Radiopaque material used in differing concentrations and routes for intravenous urography, venography, and cardiography, and for gastrointestinal visualization

METHYLGLUCAMINE DIATRIZOATE AND IODIPAMIDE
Trade name Duografin (Squibb)
Administration Intravenous
Dosage form Vial, 50% solution

METHYLHEXAMINE
Trade name Forthane (Lilly)
Administration Intranasal
Dosage form Inhaler

6 METHYLMERCAPTOPURINE
Not available on the commercial drug market

METHYLOSE (Rowell)
Trade name for Methylcellulose

METHYLPARAFYNOL
Trade name Dormison (Schering)
Administration Oral
Dosage form Capsules, 0 25 and 0 5 Gm

METHYLPHENIDATE HCl
Trade name Ritalin HCl (Ciba)
Administration Oral
Dosage form Tablets, 5, 10, and 20 mg

METHYLPHENYLETHYLHYDANTOIN
Synonym Phenantoin
Trade name Mesantoin (Sandoz)
Administration Oral
Dosage form Tablet, 100 mg

METHYLPHENYLSUCCINIMIDE
Synonym Phensuximide
Trade name Milontin (Parke, Davis)
Administration Oral
Dosage form Capsule, 0 5 Gm

METHYLPREDNISOLONE
Trade name Medrol (Upjohn)
Administration Oral
Dosage form Tablet, 4 mg

METHANTHELINE Br
Trade name Banthine Br (Searle)
Administration Oral, intramuscular, intravenous
Dosage forms Tablet, 50 mg, ampule, 50 mg

METHAPHENILENE HCl
Trade name Diatrine HCl (Warner)
Administration Oral
Dosage form Tablet, 50 mg

METHAPYRILENE
Sold over the counter under a variety of trade names Dormin, Lullamin, Nytol Sleep-Eze Somnicaps, etc.

METHAPYRILENE HCl
Synonym Thenylpyramine
Trade names Cohistine (Pitman Moore), Dormin (Dormin), Histadyl (Lilly), Lullamin (Reed & Carnrick) Methoxylene (McNeil), Semikon (Massengill), Somnicaps (Am Pharm), Thenylene (Abbott), and many others
Administration Oral topical subcutaneous intramuscular
Dosage forms Tablets 25 50 and 100 mg solutions, 1, 2, and 5% ointment, 5%

METHARBITAL
Trade name Gemonil (Abbott)
Administration Oral
Dosage form Tablet 100 mg

METHAZOLAMIDE
Trade name Neptazane (Lederle)
Administration Oral
Dosage form Tablet, 50 mg

METH DIA MER-SULFONAMIDES
Synonym Sulfamethazine Sulfadiazine Sulfamerazine Mixture
Trade names Lipo Triazine (Donley Evans), Metha merdiazine (McNeil), Neotrizine (Lilly) Sulfa tri azine (Thompson), Sulfonsol (National) Sulfose (Wyeth) Terfonyl (Squibb) Trifonamide (VanPelt & Brown), Trionamide (Flint Eaton), Tripazine (Eaton), Trisem (Massengill), Tri Sulfameth (Arlington), Trisulfazine (Central) Truozine (Abbott)
Administration Oral
Dosage forms Tablets 0 3, 0 5 Gm, fluids of various strengths

METHDILAZINE
Trade name Tacaryl (Mead Johnson)
Administration Oral
Dosage form Tablets, 4 8 mg

METHEDRINE HCl (Burroughs Wellcome)
Trade name for Methamphetamine HCl

METHENAMINE
Trade names Uritone (Parke, Davis), Urotropin (Warner Chilcott)
Administration Oral
Dosage form Tablets, 0 3 and 0 5 Gm

METHENAMINE MANDELATE
Trade name Mandelamine (Nepera)
Administration Oral
Dosage form Tablet, 0 25 Gm

METHERGINE TARTRATE (Sandoz)
Trade name for Methylergonovine Tartrate

METHIACIL (Schwartz)
Trade name for Methylthiouracil

METHIMAZOLE
Trade name Tapazole (Lilly)
Administration Oral
Dosage form Tablets 5 and 10 mg

METHIODAL SODIUM
Trade name Skiodan Sodium (Winthrop)
Administration Intravenous and retrograde
Dosage forms Tablets, 1 Gm powder solution, 40%

METHIONINE
Trade name Meonine (Wyeth)
Administration Oral and intravenous
Dosage forms Tablet, 0 5 Gm capsule, 0 2 Gm crystals

METHITURAL SODIUM
Trade name Neraval Sodium (Schering)
Administration Intravenous
Dosage form Ampule, 1 2, 5 Gm

METHIUM Cl
Trade name for Hexamethonium Cl

METHOCARBAMOL
Trade name Robaxin (Robins)
Administration Oral
Dosage form Tablet, 0 5 Gm

METHOSTAN (Schering)
Trade name for Methandriol

METHOTREXATE (Lederle)
Trade name for Amethopterin

METHOXAMINE HCl
Trade name Vasoxyl (Burroughs Wellcome)
Administration Intramuscular, intravenous
Dosage form Solution 20 mg per ml

METHOXSALEN
Trade names Meloxine (Upjohn), Oxsoralen (Elder)
Administration Topical oral
Dosage forms Tablet, 10 mg lotion 1%

MONOBENZONE
Trade name Benoquin (Elder)
Administration Topical
Dosage forms Ointment, 20% lotion 5%

MONOBROMOSALICYL ALCOHOL
Trade name Bromsalizol (Hynson)
Administration Oral intramuscular
Dosage forms Tablet, 0 3 Gm vial 40 mg per ml

MONOCAINE HCl (Novocol)
Trade name for Butethamine HCl

MONOCILLIN (Schenley)
Trade name for Procaine Penicillin G

MONODRAL Br (Winthrop)
Trade name for Penthienate Br

MONOMESTROL (Wallace & Tiernan)
Trade name for Mestilbol

MONOPHEN (Bell Craig)
Trade name for Hydroxy-diiodobenzyl cyclo hexane Carboxylic Acid

MONOTHEAMIN (Lilly)
Trade name for Theophyll ne Monoethanol amine

MONOXYCHLOROSENE
Trade name Chlorpactin (Guardian)
Administration Topical
Dosage form As such

MORNIDINE (Searle)
Trade name for Pipamizine

MORPHINE HCl
Administration Oral parenteral
Dosage forms Various forms

MORPHINE SO
Administration Oral
Dosage forms Various forms

MORPHOLINYLETHYLMORPHINE
Synonym Pholcodine
Not available on the commercial drug market

MORUSUL (Endo)
Trade name for Sodium Morrhuate

MOSIDAL (Abbott)
Trade name for Methallatal

MUCILOSE (Winthrop)
Trade name for Psyllium

MUCIN ALUMINUM HYDROXIDE MAGNESIUM TRISILICATE MIXTURE
Trade name Mucotin (Harrower)
Administration Oral
Dosage form Tablet 0 9 Gm

MUCOTIN (Harrower)
Trade name for Mucin Aluminum Hydroxide Magnesium Trisilicate Mixture

MUL-SOL (Waynor)
Detergent cleanser

MULSOPAQUE (Lafayette)
Trade name for Iophendylate

MULTIFUGE CITRATE (Blue Line)
Trade name for Piperaz ne Citrate

MURACIL (Organon)
Trade name for Methylthiouracil

MUREL (Ayerst)
Trade name for Valethamate Br

MURIAMIC (Pitman Moore)
Trade name for Glutamic Acid HCl

MUSTARGEN HCl (Merck)
Trade name for Mechloretham ne HCl

MYANESIN (Biorganic)
Trade name for Mephenes n

MY B DEN (Bischoff)
Trade name for Adenos ne Monophosphate

MYCIFRADIN SO (Upjohn)
Trade name for Neomycin SO

MYCOSTATIN (Squibb)
Trade name for Nystatin

MYLERAN (Burroughs Wellcome)
Trade name for Busulfan

MYOCARDONE (Chemical)
Trade name for Heart Muscle Extract

MYOCHRYSINE (Merck)
Trade name for Gold Sodium Thiomalate

MYOFLEX (Warren Teed)
Trade name for Triethanolamine Sal cylate

MYOXANE (Ascher)
Trade name for Mephenesin

MYSOLINE (Ayerst)
Trade name for Primidone

METHYLROSANILINE Cl
Synonym Gentian Violet
Trade name Gentersal (Ortho)
Administration Topical
Dosage forms Many forms

METHYLSALICYLATE
Synonym Oil of Wintergreen
Administration Topical
Dosage form As such

METHYLTESTOSTERONE
Trade names Andrometh (Central), Masenone (Schieffelin), Metandren (Ciba), Neo Homoreol (M) *(Organon)*, Oreton M (Schering), Synandrets (Pfizer), Synandrotabs (Pfizer)
Administration Oral, sublingual
Dosage form Tablets, 10 and 25 mg

METHYLTHIOURACIL
Trade names Methiacil (Schwartz), Muracil (Organon), Thimecil (Physicians)
Administration Oral
Dosage form *Tablet 50 mg*

METHYPRYLON
Trade name Noludar (Roche)
Administration Oral
Dosage forms Tablets 50 and 200 mg, capsule, 300 mg, elixir 12.5 mg per ml

METICORTELONE (Schering)
Trade name for Prednisolone

METICORTELONE SOLUBLE (Schering)
Trade name for Prednisolone Sodium Hemisuccinate

METICORTEN (Schering)
Trade name for Prednisone

METI DERM AEROSOL (Schering)
Trade name for Prednisolone

METOPON HCl
Administration Oral
Dosage form Capsule 3 mg

METRAZOL (Bilhuber Knoll)
Trade name for Pentylenetetrazol

METROPINE (Strasenburgh)
Trade name for Methyl Atropine NO

METUBINE I (Lilly)
Trade name for Dimethyl Tubocurarine I

METYCAINE HCl (Lilly)
Trade name for Piperocaine HCl

MICOFUR (Eaton)
Trade name for Nifuroxime

MIDICEL (Parke, Davis)
Trade name for Sulfamethoxypyridazine

MIGESTERONE (Durst)
Trade name for Progesterone

MIKEDIMIDE (Panray)
Trade name for Bemegride

MILD MERCUROUS Cl
Synonym Mercurous Cl
Administration Oral
Dosage form Tablet, 10 mg

MILIBIS (Winthrop)
Trade name for Glycobiarsol

MILK OF MAGNESIA
Synonym for Magnesium Hydroxide

MILK OF TRINESIUM (Abbott)
Trade name for Magnesium Trisilicate and Aluminum Hydroxide

MILK SUGAR
Synonym for Lactose

MILONTIN (Parke, Davis)
Trade name for Methylphenylsuccinimide

MILTOWN (Wallace)
Trade name for Meprobamate

MINERAL OIL
Synonym for Petrolatum

MINTACOL
Not available on the commercial drug market

MIOKON (Mallinckrodt)
Trade name for Sodium Dipropionamido triiodobenzoate

MIRADON (Schering)
Trade name for Anisindione

MODERIL (Pfizer)
Trade name for Rescinnamine

MOEBIQUIN (C.M.C.)
Trade name for Diiodohydroxyquin

MOLOFAC (Squibb)
Trade name for Dioctyl Sodium Succinate

MONACETIN
Not readily available on commercial drug market

MONITAN (Ives Cameron)
Trade name for Polysorbate 80

NEOHETRAMINE (Nepera)
Trade name for Thonzylamine HCl

NEO HOMBREOL (Organon)
Trade name for Testosterone Propionate

NEO HOMBREOL (F) (Organon)
Trade name for Testosterone

NEO HOMBREOL (M) (Organon)
Trade name for Methyltestosterone

NEOHYDRIN (Lakeside)
Trade name for Chlormerodrin

NEO IOPAX (Schering)
Trade name for Sodium Iodomethamate

NEOLIN (Lilly)
Trade name for Benzathine Penicillin G

NEOMYCIN SO
Trade name Mycifradin SO (Upjohn)
Administration Topical oral intramuscular
Dosage forms As such tablet 0 5 Gm. ampule 0 5 Gm

NEONAL (Abbott)
Trade name for Butethal

NEOPRONTOSIL (Winthrop)
Trade name for Azosulfamide

NEO SILVOL (Parke Davis)
Trade name for Silver I Colloidal

NEOSTAM (Burroughs Wellcome)
Trade name for Stibamine Glucoside

NEOSTENE (Miller)
Trade name for Methandriol

NEOSTIGMINE Br
Trade name Prostigmin Br (Roche)
Administration Oral ophthalmic
Dosage forms Tablet, 15 mg solution 5%

NEOSTIGMINE METHYLSULFATE
Trade name Prostigmin Methylsulfate (Roche)
Administration Subcutaneous intramuscular
Dosage form Ampules 0 25, 0 5, and 1 0 mg per ml

NEO SYNEPHRINE HCl (Winthrop)
Trade name for Phenylephrine HCl

NEOTRIZINE (Lilly)

NETHAPHYLLIN (Leeming)
Each tablet contains Isoproterenol 10 mg Theophylline, 130 mg Ephedrine SO 25 mg Phenobarbital 8 mg

NEPTAZANE
Trade name for Methazolamide

NERAVAL SODIUM (Schering)
Trade name for Methitural Sodium

NESACAINE HCl (Maltbie)
Trade name for Chloroprocaine HCl

NETHAMINE HCl (Merrell)
Trade name for Ethylephedrine HCl

NEUTRAPEN (Schenley)
Trade name for Penicillinase

NEUTRAZYME (Smith Dorsey)
Trade name for Sodium Lauryl SO

NIACIN
Synonym for Nicotinic Acid

NIACINAMIDE
Synonym for Nicotinamide

NIADRIN (Endo)
Trade name for Isoniazid

NIALAMIDE
Trade name Niamid (Pfizer)
Administration Oral
Dosage form Tablets, 25 100 mg

NIAMID (Pfizer)
Trade name for Nialamide

NICONYL (Parke Davis)
Trade name for Isoniazid

NICOTINAMIDE
Synonym Niacinamide
Administration Oral parenteral
Dosage forms Tablets 25 50 and 100 mg ampules 10 50 and 100 mg per ml

NICOTINIC ACID
Synonym Niacin
Administration Oral parenteral
Dosage form Tablets 25 50 and 100 mg

NICOZIDE (Premo)
Trade name for Isoniazid

NIFUROXIME
Trade name Micofur (Eaton)
Administration Intravaginal
Dosage forms Powders solutions and sup po... es mixed with Furazolidone

MYSTECLIN (Squibb)
Trade name for Tetracycl ne and Nystat n

MYSTECLIN V (Squibb)
Trade name for Tetracycl ne PO Complex and Nystatin M xture

MYTELASE Cl (Winthrop)
Trade name for Ambenon um Cl

NABADIAL (Breon)
Trade name for Methandr ol

NAEPAINE HCl
Trade name Amylsine HCl (Novocol)
Adm nistration Top cal
Do age form Solut on 4%

NA GENT (Raymer)
Trade name for Sodium Gent sate

NAIR (Wallace)
Proprietary depilatory

NALLINE HCl (Merck)
Trade name for Nalorph ne HCl

NALORPHINE HCl
Trade names Lethidrone (Burroughs Well come) Nalline (Merck)
Administration Intravenous, intramuscular
Dosage form Ampules 1 and 2 ml contain ing 5 mg per ml

NANDROLONE PHENPROPIONATE
Trade name Durabol n (Organon)
Administration Subcutaneous intramuscular
Dosage form Ampule 25 mg per ml

NAPENTAL (Massengill)
Trade name for Pentobarb tal Sod um

NAPHAZOLINE HCl
Trade name Pr vine HCl (Ciba)
Adm n stration Intranasal conjunct val
Dosage form Solut ons 0 05 and 0 1%

NAPRYLATE (Strasenburgh)
Trade name for Capryl c Compound

NARCOTINE
Synonym for Noscap ne

NARDIL (Warner-Ch lcott)
Trade name for Phenelzine D hydrogen SO

NARONE (Ulmer)
Trade name for D pyrone

NARTATE (Harvey)
Trade name for D pyrone

NATOLONE (National)
Trade name for Pregnenolone

NATRASCORB (U S Vitamin)
Trade name for Ascorbate Sodium

NATRINIL (National Drug)
Trade name for Carboxylic Res n

NAUCAINE (Taylor)
Trade name for Cl nocaine HCl

NEBS (Norwich)
Trade name for Acetam nophen

NEBU PREL (Mahon)
Trade name for Isoproterenol and Phenyl ephedrine Mixture

NECTADON (Merck)
Trade name for Noscap ne

NEGATAN (Lilly)
Trade name for Negatol

NEGATOL
Trade name Negatan (Lilly)
Adm n stration Intravaginal
Dosage forms Solution 45% suppos tory 5%

NEKO GERMICIDAL SOAP (Parke Davis)
Mercuric Iod de soap

NEMBUTAL (Abbott)
Trade name for Pentobarb tal Sod um

NEO A* FIL (Texas Pharmacal)
D gallol Tr oleate Cream

NEO ANTERGAN (Merck)
Trade name for Pyrilamine Maleate

NEOANTIMOSAN
Synonym for St bophen

NEOATOPHAN
Synonym for Neoc nchophen

NEOBASE (Burroughs Wellcome)
Trade name for O/W emulsion base

NEO CALGLUCON (Sandoz)
Trade name for Calcium Gluconogalactoglu conate

NEOCINCHOPHEN
Synonym Neoatophan
Trade name Tolysin (Lederle)
Adm nistration Oral
Dosage form Tablets 0 2 and 0 3 Gm

NOVATRIN (Campbell)
Trade name for Homatropine Methylbromide

NOVOBIOCIN SODIUM
Trade name Albamycin Sodium (Upjohn), Cathomycin Sodium (Merck)
Administration Oral
Dosage form Capsule, 250 mg

NOVOCAIN (Winthrop)
Trade name for Procaine HCl

NPH ILETIN (Lilly)
Trade name for Isophane Insulin

NPH INSULIN
Synonym for Isophane Insulin

NUJOL (Esso)
Trade name for Petrolatum

NU KOL-TAR (Benet)
Crude Coal Tar

NUMORPHAN HCl (Endo)
Trade name for Oxymorphone

NUPERCAINE HCl (Ciba)
Trade name for Dibucaine HCl

NUPORALS (Ciba)
Trade name for Dibucaine HCl

NYDRAZID (Squibb)
Trade name for Isoniazid

NYLIDRIN HCl
Trade name Arlidin (Arlington)
Administration Oral, subcutaneous intramuscular
Dosage forms Tablet 6 mg, ampule, 5 mg per ml

NYLOXIN (Hynson)
Trade name for Cobra Venom Preparation

NYSTATIN
Trade name Mycostatin (Squibb)
Administration Oral
Dosage form Tablet 500 000 units

NYTOL
Trade name for Methapyrilene

OBSTETRICAL PITUITRIN (Parke, Davis)
Trade name for Posterior Lobe Pituitary Extract

OCTIN HCl (Bilhuber Knoll)
Trade name for Isometheptene

OCTRITE (Hynson)
Trade name for Octyl Nitrite

OCTYL NITRITE
Trade names Medihaler Nitro (Riker) Octrite (Hynson)
Administration Inhalation
Dosage form Inhaler containing 2 ml

OENETHYL HCl (Bilhuber Knoll)
Trade name for Methylaminoheptane HCl

OIL OF WINTERGREEN
Synonym for Methylsalicylate

OILATUM (Stiefel)
Superfatted soap

OLEANDOMYCIN PO₄
Trade name Matromycin (Pfizer)
Administration Oral intravenous
Dosage form Capsule, 250 mg ampule 500 mg
Remarks Sold and dispensed largely in a mixture with Tetracycline under the proprietary name of Sigmamycin

OLEOVITAMIN A
Synonym Vitamin A
Trade names Afaxin (Winthrop), Apexol (Roerig), and many others
Administration Oral intramuscular
Dosage forms Capsules and containers of 25 to 100 000 units, ampules 25 000, 50 000 100 000 units per ml

OMNOPON
Synonym for Pantopon (Roche)

OPHTHAINE (Squibb)
Trade name for Proparacaine HCl

OPIUM
Administration Oral
Dosage forms Camphorated Tr (Paregoric), Deodorized Tr

ORABILEX (Fougera)
Trade name for Bunamiodyl

ORADIOL (VanPelt & Brown)
Trade name for Ethinyl Estradiol

ORA LUTIN (Parke, Davis)
Trade name for Ethisterone

ORANIXON (Organon)
Trade name for Mephenesin

ORAPEN (Schenley)
Trade name for Potassium Penicillin G

NIKETHAMIDE
Trade names Coramine (Ciba) Nikethyl (Abbott)
Administration Intravenous
Dosage form Ampules 250 mg per ml

NIKETHYL (Abbott)
Trade name for Nikethamide

NILEVAR (Searle)
Trade name for Norethandrolone

NILODIN
Synonym for Miracil D

NIONATE (Nion)
Trade name for Ferrous Gluconate

NISENTIL HCl (Roche)
Trade name for Alphaprodine HCl

NISULFAZOLE (Breon)
Trade name for p-Nitrosulfathiazole

NITRANITOL (Merrell)
Trade name for Mannitol Hexanitrate

NITRETAMIN (Squibb)
Trade name for Aminotrate

NITRIC ACID
Administration Topical
Dosage form Fuming acid

NITROFURANTOIN
Trade name Furadantin (Eaton)
Administration Oral, intravenous drip
Dosage form Tablet 50 mg

NITROGEN MUSTARD
Synonym for group of drugs which includes Mechlorethamine

NITROGLYCERIN
Synonym for Glyceryl Trinitrate

NITROGLYN (Key)
Delayed release tablet 2.5 to 5 mg of Glyceryl Trinitrate

NITROMERSOL
Trade name Metaphen (Abbott)
Administration Topical
Dosage forms Solution 0.5 0 0.01 0.033%, tincture 0.5%

NITROTALANS (Maney)
Trade name for Pentaerythritol Tetranitrate

p-NITROSULFATHIAZOLE
Trade name Nisulfazole (Breon)
Administration Intrarectal
Dosage form Suspension 10%

NITROUS OXIDE
Administration Inhalation
Dosage form Cylinders as such

NIVEA CREAM (Duke)
Detergent cleanser

NIVEA SKIN OIL (Duke)
Detergent cleanser

NOCTEC (Squibb)
Trade name for Chloral Hydrate

NOLUDAR (Roche)
Trade name for Methyprylon

NORETHANDROLONE
Trade name Nilevar (Searle)
Administration Oral
Dosage form Tablet 10 mg

NORETHINDRONE
Trade name Norlutin (Parke Davis)
Administration Oral
Dosage form Tablet 5 mg

NORETHYNODREL
Trade name Enovid (Searle)
Administration Oral
Dosage form Tablet 10 mg

NORFLEX (Riker)
Trade name for Orphenadrine Citrate

NORISODRINE SO (Abbott)
Trade name for Isoproterenol SO

NORLUTIN (Parke Davis)
Trade name for Norethindrone

NORMADRINE (VanPelt & Brown)
Trade name for Methamphetamine HCl

NORMAL HUMAN PLASMA
Administration Intravenous
Dosage form As such or for reconstitution

NORODIN (Endo)
Trade name for Methamphetamine HCl

NOSCAPINE
Synonym Narcotine
Trade name Nectadon (Merck)
Administration Oral
Dosage form As such

NOSTYN (Ames)
Trade name for Ectylurea

NOVALDIN (Winthrop)
Trade name for Dipyrone

OXYQUINOLINE SO_4
Trade name Chinosol (Jewell)
Administration Topical
Dosage form As such

OXYTETRACYCLINE
Trade names Terrabon (Pfizer), Terramycin (Pfizer)
Administration Oral, topical
Dosage forms Capsules, 50, 100 mg, solution troches, 15 mg aerosol, 50 mg per ml

OXYTETRACYCLINE HCl
Trade name Terramycin HCl (Pfizer)
Administration Oral, parenteral, topical
Dosage forms Solution, elixirs, drops, ointments of several concentrations

OXYTOCIN
Trade name Pitocin (Parke, Davis)
Administration Intramuscular, subcutaneous
Dosage form Ampule, 10 units per ml

P^{32}
Synonym for Sodium Radio-Phosphate

PABA SODIUM
Synonym for Sodium Para aminobenzoate

PACATAL ACETATE (Warner-Chilcott)
Trade name for Mepazine Acetate

PACATAL HCl (Warner-Chilcott)
Trade name for Mepazine HCl

PACKER'S TAR SHAMPOO (Packer)
Tar shampoo

PACKER'S TAR SOAP (Packer)
Pine tar soap

PADUTIN (Winthrop)
Trade name for Pancreatic Gland Extract
Administration Parenteral

PAGITANE HCl (Lilly)
Trade name for Cycrimine HCl

PALUDRINE HCl (Ayerst)
Trade name for Chloroguanide HCl

PAM
Synonym for Pyridine Aldoximine Methiodine

PAMAQUINE NAPHTHOATE
Synonym Plasmoquine
Trade name Plasmochin Naphthoate (Winthrop)
Administration Oral
Dosage form Tablets, 20 and 40 mg

PAMINE Br (Upjohn)
Trade name for Methscopolamine Br

PAMISYL (Parke, Davis)
Trade name for Aminosalicylic Acid

PAMISYL SODIUM (Parke, Davis)
Trade name for Sodium Aminosalicylate

PANALBA (Upjohn)
Trade name for mixture of Tetracycline PO_4 and Novobiocin Sodium

PANCREATIC DORNASE
Trade name Dornavac (Merck)
Administration Inhalation
Dosage form Vial, when reconstituted 50,000 U per ml

PANCREATIN
Trade names Amylgestin (McNeil), Panopsin (Harrower), Viokase (Vio-Bin)
Administration Oral
Dosage forms A variety of forms and sizes

PANHEPRIN (Abbott)
Trade name for Heparin Sodium

PANMYCIN (Upjohn)
Trade name for Tetracycline

PANMYCIN HCl (Upjohn)
Trade name for Tetracycline HCl

PANMYCIN PO_4 (Upjohn)
Trade name for Tetracycline PO_4 Complex

PANOPSIN (Harrower)
Trade name for Pancreatin

PANPARNIT (Geigy)
Trade name for Caramiphen HCl

PANRONE (Panray)
Trade name for Amithiozone

PANTHOLIN (Lilly)
Trade name for Pantothenic Acid

PANTOPAQUE (Lafayette)
Trade name for Iophendylate

PANTOPIUM
Synonym for Pantopon (Roche)

PANTOPON (Roche)
Proprietary mixture of opium alkaloids, principally morphine
Synonyms Omnopon, Pantopium
Administration Oral, subcutaneous
Dosage forms Tablets, approximately 10, 20 mg, ampule, approximately 20 mg per ml

ORESTRALYN (McNeil)
Trade name for Ethinyl Estrad ol

ORETIC (Abbott)
Trade name for Hydrochlorothiazide

ORETON (Schering)
Trade name for Testosterone Propionate

ORETON F (Schering)
Trade name for Testosterone

ORETON M (Schering)
Trade name for Methyltestosterone

ORGANIDIN (Wampole)
Trade name for Iod nated Glycerol

ORINASE (Upjohn)
Trade name for Tolbutamide

ORPHENADRINE CITRATE
Trade name Norflex (Riker)
Administration Oral
Dosage form Tablet 100 mg

ORPHENADRINE HCl
Trade name D s pal (Riker)
Administration Oral
Dosage form Tablet 50 mg

ORTHOXINE HCl (Upjohn)
Trade name for Methoxyphenamine HCl

OSTENSIN (Wyeth)
Trade name for Trimethid nium Methosulfate

OTOSONE F (Broemmel)
Trade name for Hydrocort sone

OTRIVIN (Ciba)
Trade name for Xylometazol ne HCl

OUABAIN
Administration Intravenous intramuscular
Dosage form Ampules of various s zes

OVOCYLIN (Ciba)
Trade name for Estradiol

OVOCYLIN BENZOATE (Ciba)
Trade name for Estrad ol Benzoate

OVOCYLIN DIPROPIONATE (Ciba)
Trade name for Estrad ol D prop onate

O/W EMULSION BASE
Synonym for Oil in Water emulsion base

OX BILE EXTRACT
Trade names Bicol (McNeil), B lein (Abbott)
Administration Oral
Dosage form Tablets of various s zes

OXALIC AND MALONIC ACID MIXTURE
Trade name Koagamin (Chatham)
Administration Parenteral
Dosage form Vial 10 ml.

OXANAMIDE
Trade name Quiactin (Merrell)
Administration Oral
Dosage form Tablet, 400 mg

OXOPHENARSINE HCl
Trade name Mapharsen (Parke Davis)
Administration Intravenous
Dosage form Ampules 40 60 mg, 0 6 Gm

OXSORALEN (Elder)
Trade name for Methoxsalen

OXTRIPHYLLINE
Synonym Chol ne Theophyllinate
Trade name Choledyl (Nepera)
Administration Oral
Dosage form Tablets 0 1 Gm, 0 2 Gm

OXUCIDE (Breon)
Trade name for Piperaz ne Citrate

OXYCEL (Parke Davis)
Trade name for Cellulose Oxidized

OXYFED (Cole)
Trade name for Methamphetamine HCl

OXYGEN
Administration Inhalation
Dosage forms Under pressure in tanks or metal bottles

OXYL-IODIDE (Lilly)
Trade name for Cinchophen Hydriod de

OXYLONE (Upjohn)
Trade name for Fluorometholone

OXYMORPHONE
Trade name Numorphan HCl (Endo)
Administration Parenteral rectal
Dosage forms Ampules 1 2, and 10 ml suppositories 2 and 5 mg

OXYPHENCYCLIMINE HCl
Trade name Daricon (Pfizer)
Administration Oral
Dosage form Tablet 10 mg

OXYPHENONIUM Br
Trade name Antrenyl Br (C ba)
Administration Oral
Dosage forms Tablet 5 mg syrup about 1 mg per ml.

OXYPOLYGELATIN SOLUTION
Synonym for Gelatin Solution, Purified

PASEM SODIUM (Massengill)
Trade name for Sodium Aminosalicylate

PASKALIUM (Glenwood)
Trade name for Potassium Aminosalicylate

PASKATE (Lilly)
Trade name for Potassium Aminosalicylate

PATHILON (Lederle)
Trade name for Tridihexethide

PAVATRINE (Searle)
Trade name for Aminocarbofluorene

PAVERIL (Lilly)
Trade name for Dioxyline

PECAZINE
Synonym for Mepazine

PECTIN
Administration Oral
Dosage form As such but mainly in mixtures

PEGANONE (Abbott)
Trade name for Ethotoin

PELLETIERINE TANNATE
Trade name Punicine Tannate (N Y Quinine)
Administration Oral
Dosage form Capsule, 0 25 Gm

PELLEX (Pellex)
Calcium Hydroxide thioglycollic acid

PEMOPHYLLIN (Pitman Moore)
Trade name for Theophylline Sodium Glycinate

PENALEV (Merck)
Trade name for Potassium Penicillin G

PENASOID (Parke Davis)
Trade name for Potassium Penicillin G

PENDIOMIDE (Ciba)
Trade name for Azamethonium Br

PEN G CAP (Upjohn)
Trade name for Procaine Penicillin G

PENICILLIN V
Synonym for Phenoxymethyl Penicillin

PENICILLINASE
Trade name Neutrapen (Schenley)
Administration Intravenous
Dosage form Vial, 800 000 units

PENTAERYTHRITOL CHLORAL
S[illegible]

PENTAERYTHRITOL TETRANITR[illegible]
Trade names Angicap (Pro-Acet), [illegible]talans (Maney) Pentritol (Evron), [illegible]trate (Warner Chilcott)
Administration Oral
Dosage forms Tablets 10 and 20 mg sustained release tablet 30 mg

PENTAL (VanPelt & Brown)
Trade name for Pentobarbital Sodium

PENTAQUINE PO
Administration Oral
Dosage form Tablet 13 3 mg

PENTHIENATE Br
Trade name Monodral Br (Winthrop)
Administration Oral
Dosage form Capsule, 5 mg

PENTIDS (Squibb)
Trade name for Potassium Penicillin G

PENTOBARBITAL SODIUM
Trade names Isobarb (U S Standa[illegible]) Napental (Massengill), Nembutal ([illegible]bott), Pental (VanPelt & Brown)
Administration Oral, rectal intravenou[illegible]
Dosage forms Capsules 30 50 100 [illegible] elixir, 3 mg per ml suppositories 30 130, and 200 mg, 0 25 and 0 5 Gm [illegible] diluted, vial 50 mg per ml

PENTOLINIUM
Trade name Ansolysen (Wyeth)
Administration Oral
Dosage form Tablets 20 40, and 100

PENTOTHAL SODIUM (Abbott)
Trade name for Thiopental Sodium

PENTRITOL (Evron)
Trade name for Pentaerythritol Tetranitr[illegible] in sustained release form

PENTYLENETETRAZOL
Trade names Cardiazol (Bilhuber Knol[illegible]) Metrazol (Bilhuber Knoll)
Administration Intravenous
Dosage form Ampules 1 and 3 ml conta[illegible]ing 0 1 Gm per ml

PENVEE (Wyeth)
Trade name for Phenoxymethyl Penicillin

PEN VEE K (Wyeth)
Trade name for Potassium Penicillin V

PEN VEE L-A (Wyeth)
Trade name for Phenoxymethyl Penicillin

PERANDREN (Ciba)
Trade name for Testosterone Propionate

PANTOTHENIC ACID
Trade name Ilopan (Warren-Teed), Panthol n (Lilly)
Administration Oral
Dosage form Tablet, 10 mg

PANTOTHENYL ALCOHOL
Trade name Ilopan (Warren Teed)
Administration Intramuscular
Dosage form 250 mg per ml

PAPAVERINE
Administration Oral
Dosage forms Tablets 0 03 0 06 0 1 and 0 2 Gm

PAPAVERINE HCl
Administration Intravenous
Dosage form Ampule 30 mg per ml

PAPAYA ENZYME
Trade name Caroid (Am Ferment)
Administration Oral
Dosage forms As such tablet 100 mg

PARA AMINOSALICYLIC ACID
Synonym for Aminosalicyl c Acid

PARABROMDYLAMINE MALEATE
Trade name Dimetane (Robins)
Administration Oral
Dosage forms Tablet, 4 mg elixir 0 4 mg per ml Extentabs, 12 mg

PARACARBINOXAMINE MALEATE
Trade name Clistin Maleate (McNeil)
Administration Oral
Dosage forms Tablet 4 mg fluid 1 25 mg per ml

PARACODIN (*Bilhuber Knoll*)
Trade name for Dihydrocodeine Bitartrate

PARACORT (Parke Davis)
Trade name for Prednisone

PARACORTOL (*Parke, Davis*)
Trade name for Prednisolone

PARADIONE (Abbott)
Trade name for Paramethad one

PARAFLEX (*McNeil*)
Trade name for Chlorzoxazone

PARALDEHYDE
Administration Oral rectal intramus ular intravenous
Dosage form As such

PARAMETHADIONE
Trade name Paradione (Abbott)
Administration Oral
Dosage forms Capsules, 150 and 300 mg solution, 0 3 Gm per ml

PARAMINYL (Buffington)
Trade name for Pyrilamine Maleate

PARANITROSULFATHIAZOLE
Trade name Nisulfazole (*Breon*)
Administration Rectal
Dosage form Suspension 10%

PARA PAS (Gold Leaf)
Trade name for Aminosalicylic Acid

PARASAL (Panray)
Trade name for Aminosalicylic Acid

PARASAL CALCIUM (Panray)
Trade name for Calcium Aminosalicylate

PARASAL SODIUM (*Panray*)
Trade name for Sodium Aminosalicylate

PARATHYROID EXTRACT
Trade name Paroidin (*Parke Davis*)
Administration Subcutaneous intramuscular
Dosage form Ampule 100 units per ml

PARAZINE CITRATE (Tutag)
Trade name for P perazine Citrate

PAREDRINE *HBr* (Smith Kline & French)
Trade name for Hydroxyamphetamine HBr

PAREGORIC
Opium preparation

PARENOGEN (Cutter)
Trade name for Fibrinogen (Human)

PARENTRACIN (C.S.C.)
Trade name for Bacitracin

PARENZYME (National)
Trade name for Trypsin

PARODYNE
Synonym for Antipyrine

PAROIDIN (Parke Davis)
Trade name for Parathyroid Extract

PARSIDOL (Warner Chilcott)
Trade name for Ethopropazine HCl

PASARA SODIUM (Smith Dorsey)
Trade name for Sod um Aminosalicylate

PHENINDAMINE TARTRATE
Trade name Thephorin (Roche)
Administration Oral topical
Dosage forms Tablet, 10 mg syrup about 2 mg per ml lotion 2% ointment 5%

PHENINDIONE
Trade names Danilone (Schieffelin) Hedulin (Walker) Indon (Parke Davis)
Administration Oral
Dosage form Tablet 50 mg

PHENIRAMINE MALEATE
Synonym Prophenpyridamine Maleate
Trade names Inhiston (Union) Trimeton (Schering)
Administration Oral
Dosage forms Tablets 25 mg elixir about 2 mg per ml

PHENMETRAZINE HCl
Trade name Preludin (Geigy)
Administration Oral
Dosage form Tablet 25 mg

PHENOBARBITAL
Trade name Luminal Sodium (Winthrop)
Administration Oral
Dosage form Tablets 15 30 and 100 mg

PHENOBARBITAL SODIUM
Trade name Luminal Sodium (Winthrop)
Administration Oral rectal intravenous intramuscular
Dosage forms Ampules containing 0 13, 0 16 and 0 3 Gm in solution and as a powder tablets 65 and 100 mg

PHENOL
Synonym Carbolic Acid
Administration Topical
Dosage forms Various forms

PHENOL RED
Synonym for Phenolsulfonphthalein

PHENOLOR (Squibb)
Trade name for Cresol

PHENOLPHTHALEIN
Trade names Too large a number to list
Administration Oral
Dosage forms A large variety of forms

PHENOLSULFONPHTHALEIN
Synonym Phenol Red P S P
Administration Intravenous intramuscular
Dosage form Ampule 6 mg per ml

PHENOXENE (Pitman Moore)
Trade name for Chlorphenoxamine HCl

PHENOXYBENZAMINE HCl
Trade name Dibenzyline (Smith Kline & French)
Administration Oral
Dosage form Capsule 10 mg

PHENOXYMETHYL HYDRABAMINE PENICILLIN
Trade name Compocillin V (Abbott)
Administration Oral
Dosage form Suspension 60 000 units per ml

PHENOXYMETHYL PENICILLIN
Synonym Penicillin V
Trade name Pen Vee L A (Wyeth) V Cillin (Lilly)
Administration Oral
Dosage form Tablets 200 000 and 500 000 units

PHENOXYMETHYL POTASSIUM PENICILLIN
Synonym for Potassium Penicillin V

PHENPROCOUMON
Trade names Liquamar (Organon) Marcumar (Roche)
Administration Oral
Dosage form Tablet 3 mg

PHENPROPAMIDE
Not available on the commercial drug market

PHENSUXIMIDE
Synonym for Methylphenylsuccinimide

PHENTETIOTHALEIN SODIUM
Trade name Iso-Iodeikon (Mallinckrodt)
Administration Intravenous
Dosage form Ampule 2 5 Gm

PHENTOLAMINE HCl
Trade name Regitine HCl (Ciba)
Administration Oral
Dosage form Tablet 50 mg

PHENTOLAMINE METHANESULFONATE
Trade name Regitine Methanesulfonate (Ciba)
Administration Intravenous intramuscular
Dosage form Ampule 5 mg

PHENURONE (Abbott)
Trade name for Phenacemide

PHENYLAZO DIAMINO PYRIDINE HCl
Trade names Azodyne (Stuart) Mallophene (Mallinckrodt) Pyridium (Merck)
Administration Oral topical
Dosage forms Tablet 100 mg solution 10 mg per ml

PERANDREN PHENYLACETATE (Ciba)
Trade name for Testosterone Phenylacetate

PERAZIL (Burroughs Wellcome)
Trade name for Chlorcyclizine HCl

PERCORTEN (Ciba)
Trade name for Desoxycorticosterone Acetate

PERFECTOCHOL (Lafayette)
Trade name for Iodoalphionic Acid

PERICLOR (Ives Cameron)
Trade name for Petrichloral

PERIN (Endo)
Trade name for Piperazine Calcium Edathamil

PERISTALTIN (Ciba)
Trade name for Cascara Sagrada

PERISTIM (Mead Johnson)
Trade name for Extract of Cascara Sagrada

PERITRATE (Warner Chilcott)
Trade name for Pentaerythritol Tetranitrate

PERMAPEN (Pfizer)
Trade name for Benzathine Penicillin G

PERMITIL (White)
Trade name for Fluphenazine Dihydrochloride

PERNAEMON (Organon)
Trade name for Liver Injection Purified

PERPHENAZINE
Trade name Trilafon (Schering)
Administration Oral
Dosage forms Tablets, 2 4, 8 and 16 mg syrup 0 4 mg per ml

PETHIDINE
Synonym for Meperidine

PETRICHLORAL
Trade name Periclor
Administration Oral
Dosage form Capsule 0 3 Gm

PETROLATUM
Synonym Mineral oil
Trade names Albolene (McKesson & Robbins) Kondremul (Patch) Nujol (Esso) Petronol (Lilly)
Administration Oral
Dosage form As such

PETRONOL (Lilly)
Trade name for Petrolatum

PHANODORN CALCIUM (Winthrop)
Trade name for Cyclobarbital Calcium

PHE-MER-NITE (Massengill)
Trade name for Phenylmercuric NO

PHEMEROL Cl (Parke Davis)
Trade name for Benzethonium Cl

PHENACAINE HCl
Synonym Holocaine HCl
Administration Topical
Dosage form Ointment 2%

PHENACEMIDE
Trade name Phenurone (Abbott)
Administration Oral
Dosage form Tablets 0 3 and 0 5 Gm

PHENACETIN
Synonym for Acetophenetidin

PHENAGLYCODOL
Trade name Ultran (Lilly)
Administration Oral
Dosage form Tablet 0 3 Gm

PHENANTOIN
Synonym for Methylphenylethylhydantoin

PHENARSONE
Trade name Aldarsone (Abbott)
Administration Intravaginal
Dosage forms Ampule 1 Gm powder suppository 0 ? Gm

PHENARSONE SULFOXYLATE
Trade name Aldarsone (Abbott)
Administration Intravenous
Dosage form Ampule 1 Gm

PHENAZONE
Synonym for Antipyrine

PHENELZINE DIHYDROGEN SO
Trade name Nardil (Warner Chilcott)
Administration Oral
Dosage form Tablet 15 mg

PHENERGAN (Wyeth)
Trade name for Promethazine HCl

PHENETSAL
Trade name Salophen (Winthrop)
Administration Oral
Dosage form Tablet 0 3 Gm

PHENFORMIN
Trade name DBI (U S Vitamin)
Administration Oral
Dosage form Tablet, 25 mg

PHYTONADIONE
Synonym Vitamin K_1
Trade names Mephyton (Merck), Konakion (Roche)
Administration Intravenous, oral
Dosage forms Ampule, 50 mg per ml, tablet, 5 mg

PICRAGOL (Wyeth)
Trade name for Silver Picrate

PICRIC ACID
Administration Topical
Dosage form Various concentrations

PICROTOXIN
Administration Intravenous
Dosage form Ampules, 1 and 20 ml containing 3 mg per ml

PIG BILE EXTRACT
Administration Oral
Dosage form Tablet, 0 25 Gm

PILOCARPINE HCl
Administration Subcutaneous
Dosage form 15 mg hypo tablets

PIPADONE
Synonym for Dipipanone

PIPAMAZINE
Trade name Mornidine (Searle)
Administration Oral intravenous
Dosage forms Tablet, 5 mg, ampule, 5 mg

PIPANOL (Winthrop)
Trade name for Trihexyphenidyl HCl

PIPENZOLATE METHYLBROMIDE
Trade name Piptal (Lakeside)
Administration Oral
Dosage form Tablet 5 mg

PIPERATE (Lincoln)
Trade name for Piperazine Tartrate

PIPERAZATE (Leeming)
Trade name for Piperazine PO_4

PIPERAZINE CALCIUM EDATHAMIL
Trade name Perin (Endo)
Administration Oral
Dosage form 100 mg per ml

PIPERAZINE CITRATE
Trade names Antepar Citrate (Burroughs Wellcome), Multifuge Citrate (Blue Line), Oxucide (Breon), Parazine Citrate (Tutag), Pipizan Citrate (Merck)
Administration Oral
Dosage forms A variety of forms

PIPERAZINE ESTRONE SO_4
Trade name Sulestrex Piperazine (Abbot
Administration Oral
Dosage forms Tablets, 0 75, 1 5, and 3 mg, elixir, 0 3 mg per ml

PIPERAZINE GLUCONATE
Trade name Vermizine (Chicago)
Administration Oral
Dosage form Syrup, 100 mg per ml

PIPERAZINE HEXAHYDRATE
Trade name Anthalazine (Bowman)
Administration Oral
Dosage form Solution, 100 mg per ml

PIPERAZINE PO_4
Trade name Piperazate (Leeming)
Administration Oral
Dosage form Wafer, 500 mg

PIPERAZINE TARTRATE
Trade name Piperate (Lincoln)
Administration Oral
Dosage form Solution, 100 mg per ml

PIPERIDOLATE HCl
Trade name Dactil (Lakeside)
Administration Oral
Dosage form Capsule, 50 mg

PIPERILATE HCl
Trade name Sycotrol (Reed & Carnrick)
Administration Oral
Dosage form Tablet, 3 mg

PIPEROCAINE HCl
Trade name Metycaine HCl (Lilly)
Administration Topical, parenteral
Dosage forms A variety of forms

PIPEROXAN HCl
Trade name Benodaine HCl (Merck)
Administration Intravenous
Dosage form Ampule, 20 mg per ml

PIPIZAN CITRATE (Merck)
Trade name for Piperazine Citrate

PIPRADROL HCl
Trade name Meratran (Merrell)
Administration Oral
Dosage form Tablets, 1 0, 2 5 mg

PIPTAL (Lakeside)
Trade name for Pipenzolate Methylbromide

PIROMEN (Travenol)
Trade name for Pseudomonas Polysaccharides

PITOCIN (Parke, Davis)
Trade name for Oxytocin

PHENYLBUTAZONE
Trade name Butazolidin (Geigy)
Administration Oral
Dosage form Tablets 100 and 200 mg

PHENYLDIMETHYLPYRAZOLON FERRIC Cl
Trade name Ferropyrin (B lhuber Knoll)
Administration Top cal
Dosage forms Powder 15% solution 20%

PHENYLEPHRINE HCl
Trade names Almefrin (Meyer) Neo-Synephrine HCl (Winthrop) Sucraphen (Smith Dorsey)
Administration Oral intranasal intramuscular, intravenous
Dosage forms Capsules 10 25 mg elixir 1 mg per ml topical preparat ons various ampules 2 and 10 mg per ml

β PHENYLISOPROPYL HYDRAZINE
Trade name Catron (Lakes de)
Administration Oral
Dosage form Tablets 3 and 6 mg

PHENYLMERCURIC BORATE
Trade name Merphenyl Borate (Hamilton)
Dosage form Tincture 0 2%

PHENYLMERCURIC NO
Trade names Merphenyl NO_3 (Hamilton Phe mer nite (Masseng ll) and others
Dosage forms Many forms

PHENYLONE
Synonym for Ant pyrine

PHENYLPROPANOLAMINE HCl
Trade name Propadrine HCl (Merck)
Administration Oral intranasal
Dosage forms Capsules 25 50 mg solu t ons 1 and 3%

PHENYLPROPYLMETHYLAMINE HCl
Trade name Vonedrine (Merrell)
Administration Inhalation topical
Dosage forms Inhaler 250 mg solution 2 8%

PHENYL-TERT BUTYLAMINE RESIN
Trade name Ionamin (Strasenburgh)
Administration Oral
Dosage form Capsules 15 and 30 mg

PHENYLTOLOXAMINE DIHYDROGEN CITRATE
Trade name Bristamin (Bristol)
Administration Oral
Dosage form Tablet 25 mg

PHENYLTOLOXAMINE RESIN COMPLEX
Trade name H st onex (Strasenburgh)
Administration Oral
Dosage form Capsules 25 50 mg

PHENYTOIN
Synonym for D phenylhydanto n Sod um

PHETHENYLATE SODIUM
Trade name Thianto n (Lilly)
Administration Oral
Dosage form Capsules 0 12 and 0 24 Gm

pHISODERM (Winthrop)
Trade name for Entsufon

pHISOHEX (Winthrop)
Trade name for Hexachlorophene Soap

PHOBEX (Lloyd)
Trade name for Benactyzine HCl

PHOLCODINE
Synonym for Morpholinylethylmorphine

PHOSFO NEFRIN (Schieffelin)
Trade name for Epinephrine PO

PHOSPHALJEL (Wyeth)
Trade name for Aluminum Phosphate Gel

PHOSPHOLINE I
Synonym Echoth ophate
Not ava lable on the commercial drug market

PHOSPHORATED CARBOHYDRATE SOLUTION
Trade name Emetrol (Kinney)
Administrat on Oral
Dosage form Solution as such

PHOSPHORIC ACID
Administration Oral
Dosage form Solution 10%

PHTHALYLSULFACETAMIDE
Trade names Talsul n (Squ bb) Thalamyd (Schering), Thal sul (Massengill)
Administration Oral
Dosage form Tablet 0 5 Gm

PHTHALYLSULFATHIAZOLE
Trade name Sulfathal dine (Merck)
Administration Oral
Dosage form Tablet 0 5 Gm

PHYLLICIN (B lhuber Knoll)
Trade name for Theophyll ne Calcium Sal cy late

PHYSOSTIGMINE SALICYLATE
Synonym *Eserine Sal cylate*
Administration Top cal (ophthalm c), subcutaneous
Dosage forms Ampule 2 mg per ml powder

PHYTONADIONE
Synonym Vitamin K_1
Trade names Mephyton (Merck), Konakion (Roche)
Administration Intravenous, oral
Dosage forms Ampule, 50 mg per ml, tablet, 5 mg

PICRAGOL (Wyeth)
Trade name for Silver Picrate

PICRIC ACID
Administration Topical
Dosage form Various concentrations

PICROTOXIN
Administration Intravenous
Dosage form Ampules, 1 and 20 ml containing 3 mg per ml

PIG BILE EXTRACT
Administration Oral
Dosage form Tablet, 0 25 Gm

PILOCARPINE HCl
Administration Subcutaneous
Dosage form 15 mg hypo tablets

PIPADONE
Synonym for Dipipanone

PIPAMAZINE
Trade name Mornidine (Searle)
Administration Oral, intravenous
Dosage forms Tablet, 5 mg, ampule, 5 mg

PIPANOL (Winthrop)
Trade name for Trihexyphenidyl HCl

PIPENZOLATE METHYLBROMIDE
Trade name Piptal (Lakeside)
Administration Oral
Dosage form Tablet 5 mg

PIPERATE (Lincoln)
Trade name for Piperazine Tartrate

PIPERAZATE (Leeming)
Trade name for Piperazine PO_4

PIPERAZINE CALCIUM EDATHAMIL
Trade name Perin (Endo)
Administration Oral
Dosage form 100 mg per ml

PIPERAZINE CITRATE
Trade names Antepar Citrate (Burroughs Wellcome), Multifuge Citrate (Blue Line), Oxucide (Breon), Parazine Citrate (Tutag), Pipizan Citrate (Merck)
Administration Oral
Dosage forms A variety of forms

PIPERAZINE ESTRONE SO_4
Trade name Sulestrex Piperazine (Abbott)
Administration Oral
Dosage forms Tablets, 0 75, 1 5, and 3 0 mg ; elixir, 0 3 mg per ml

PIPERAZINE GLUCONATE
Trade name Vermizine (Chicago)
Administration Oral
Dosage form Syrup, 100 mg per ml

PIPERAZINE HEXAHYDRATE
Trade name Anthalazine (Bowman)
Administration Oral
Dosage form Solution, 100 mg per ml

PIPERAZINE PO_4
Trade name Piperazate (Leeming)
Administration Oral
Dosage form Wafer, 500 mg

PIPERAZINE TARTRATE
Trade name Piperate (Lincoln)
Administration Oral
Dosage form Solution, 100 mg per ml

PIPERIDOLATE HCl
Trade name Dactil (Lakeside)
Administration Oral
Dosage form Capsule, 50 mg

PIPERILATE HCl
Trade name Sycotrol (Reed & Carnrick)
Administration Oral
Dosage form Tablet, 3 mg

PIPEROCAINE HCl
Trade name Metycaine HCl (Lilly)
Administration Topical, parenteral
Dosage forms A variety of forms

PIPEROXAN HCl
Trade name Benodaine HCl (Merck)
Administration Intravenous
Dosage form Ampule, 20 mg per ml

PIPIZAN CITRATE (Merck)
Trade name for Piperazine Citrate

PIPRADROL HCl
Trade name Meratran (Merrell)
Administration Oral
Dosage form Tablets, 1 0, 2 5 mg

PIPTAL (Lakeside)
Trade name for Pipenzolate Methylbromide

PIROMEN (Travenol)
Trade name for Pseudomonas Polysaccharides

PITOCIN (Parke, Davis)
Trade name for Oxytocin

PITRESSIN *(Parke Davis)*
Trade name for Vasopressin

PITRESSIN TANNATE (Parke Davis)
Trade name for Vasopressin Tannate

PITUITARY EXTRACT (POSTERIOR)
Synonyms Pituitary Obstetrical Pituitary Surgical
Trade names Infundin (Burroughs Wellcome) Pitutrin (Parke Davis)
Administration Intramuscular subcutaneous
Dosage form Ampules 5 and 10 units per ml

PITUITARY GONADOTROPIN
Trade names Equiphysin (Harvey) Gonado Trone (Miller)
Administration Subcutaneous intramuscular
Dosage forms Ampule varying dosages

PITUITRIN (Parke Davis)
Trade name for Pituitary Extract (Posterior)

PLACIDYL (Abbott)
Trade name for Ethchlorvynol

PLANTAGO
Trade names L A Formula (Burton Parsons) Konsyl (Burton Parsons)
Administration Oral
Dosage forms A variety of forms

PLAQUENIL SO₄
Trade name for Hydroxychloroquine SO

PLASMOCHIN NAPHTHOATE (Winthrop)
Trade name for Pamaquine Naphthoate

PLASMOQUINE
Synonym for Pamaquine Naphthoate

PLAVOLEX (Wyeth)
Trade name for Dextran

PLAZMOID (Upjohn)
Trade name for Gelatin Solution Purified

PLECYAMIN 12 (Plessner)
Trade name for Cyanocobalamin

PM 396
Synonym for Methsuximide

PODOPHYLLIN
Administration Topical
Dosage form Ointment, 25%

POLARAMINE (Schering)
Trade name for Dextro-chlorpheniramine

POLOXALKOL
Trade name Polykol (Upjohn)
Administration Oral
Dosage form Liquid 200 mg per ml

POLYAMINE METHYLENE RESIN
Trade names Exorbin (Ayerst) Resinat (National) Basex (Columbus)
Administration Oral
Dosage form Tablet 0 25 Gm

POLYBRENE (Abbott)
Trade name for Hexadimethrine Br

POLYCYCLINE (Bristol)
Trade name for Tetracycline

POLYCYCLINE HCl (Bristol)
Trade name for Tetracycline HCl

POLYESTRADIOL PO
Trade name Estradurin (Ayerst)
Administration Intramuscular
Dosage form Vial 40 mg

POLYETHYLENE GLYCOLS
Carbowax 400 Carbowax 1000 Carbowax 1500 Carbowax 1540 Carbowax 4000 (all Carbide and Carbon)

POLYKOL (Upjohn)
Trade name for Poloxalkol

POLYMYXIN B SO₄
Trade name Aerosporin (Burroughs Wellcome)
Administration Oral intramuscular intrathecal topical
Dosage forms Vials 200 000 and 500 000 units tablet 500 000 units

POLYOXYETHYLENE 20
Synonym for Polysorbate 80

POLYSORB HYDRATE (Fougera)
Trade name for Sorbitan Sesquioleate Emulsion

POLYSORBATE 20
Synonyms Sorbitan Monolaurate Tween 20 Emulsifier

POLYSORBATE 80
Synonyms Polyoxyethylene 20, Sorbitan Mono-oleate Tween 80
Trade names Monitan (Ives Cameron) Sorlate (Abbott)

POLYVINYLPYRROLIDONE
Trade name PVP Macrose (Schenley)
Administration Intravenous
Dosage form Bottle, 3 5%

PONTOCAINE HCl (Winthrop)
Trade name for Tetracaine HCl

POQUIL (Parke, Davis)
Trade name for Pyrvinium Cl

POSTAFENE
Synonym for Meclizine HCl

POSTERIOR LOBE PITUITARY EXTRACT
Trade names Obstetrical Pituitrin (Parke, Davis), Surgical Pituitrin (Parke, Davis)
Administration Subcutaneous, intramuscular
Dosage form Ampule, 10, 20 units per ml

POTASSIC SALINE
Synonym for Darrow's Solution

POTASSIUM ACETATE
Administration Intravenous, oral
Dosage form Ampule and powder

POTASSIUM AMINOSALICYLATE
Synonym Potassium Para aminosalicylate
Trade names Paskalium (Glenwood), Paskate (Lilly)
Dosage forms Tablet, 0 5 Gm , powder

POTASSIUM AND SODIUM CHLORIDE WITH SODIUM LACTATE SOLUTION
Synonym for Darrow's Solution (Modified)

POTASSIUM ARSENITE
Synonym Fowler's Solution
Administration Oral
Dosage form Solution, 1%

POTASSIUM BICARBONATE
Administration Oral
Dosage form Powder

POTASSIUM CITRATE
Administration Oral
Dosage forms Various solutions

POTASSIUM Cl
Administration Oral, intravenous
Dosage forms Crystals, ampules of varying concentration, often concentrated as 1 75 mEq per ml to be diluted at least 50 times in infusion fluid

POTASSIUM Cl IN DEXTROSE
Trade name Kadalex (Don Baxter)
Administration Intravenous
Dosage form Bottle, 0 2% in 5% dextrose

POTASSIUM GLUCONATE
Trade name Kaon (Warren Teed)
Administration Oral
Dosage form Elixir, 50 mg potassium per ml

POTASSIUM I
Trade name Enkide (Brewer)
Administration Oral
Dosage forms A large variety of forms

POTASSIUM PARA-AMINOSALICYLATE
Synonym for Potassium Aminosalicylate

POTASSIUM PENICILLIN
Available in ointments

POTASSIUM PENICILLIN G
Trade names Dramcillin (White), Drop- [illegible]
Administration Oral, parenteral
Dosage forms A large variety of forms

POTASSIUM PENICILLIN O
Trade name Cer-O Cillin Potassium (Upjohn)
Administration Oral, topical, parenteral
Dosage forms Tablet, 100,000 units, troche, 5,000 units, ampule, 200,000 units per ml

POTASSIUM PENICILLIN V
Synonym for Phenoxymethyl Potassium Penicillin

POTASSIUM PERMANGANATE
Administration Lavage
Dosage forms Tablets and crystals

POTASSIUM PHENOXYMETHYL PENICILLIN
Synonym Potassium Penicillin V
Trade name Compocillin-VK Potassium (Abbott)
Administration Oral
Dosage forms Tablets, 125 and 250 mg , granules for solution

POTASSIUM PO_4
Administration Intravenous
Dosage form Ampule

POTASSIUM THIOCYANATE
Administration Oral
Dosage form Tablet, 0 2 Gm

POVAN (Parke, Davis)
Trade name for Pyrvinium Pamoate

POVIDONE IODINE COMPLEX
Trade names Betadine (Carbin & Conwell), Isodine (Isodine)
Dosage form 1% to be diluted

PRAGMATAR (Smith, Kline & French)
Tar sulfur salicyclic acid ointment

PITRESSIN (Parke Davis)
Trade name for Vasopressin

PITRESSIN TANNATE (Parke, Davis)
Trade name for Vasopressin Tannate

PITUITARY EXTRACT (POSTERIOR)
Synonyms Pituitary, Obstetrical Pituitary Surgical
Trade names Infundin (Burroughs Wellcome), Pituitrin (Parke, Davis)
Administration Intramuscular subcutaneous
Dosage form Ampules, 5 and 10 units per ml

PITUITARY GONADOTROPIN
Trade names Equ physin (Harvey), Gonado Trone (Miller)
Administration Subcutaneous intramuscular
Dosage forms Ampule varying dosages

PITUITRIN (Parke Davis)
Trade name for Pituitary Extract (Posterior)

PLACIDYL (Abbott)
Trade name for Ethchlorvynol

PLANTAGO
Trade names L A Formula (Burton Parsons) Konsyl (Burton Parsons)
Administration Oral
Dosage forms A variety of forms

PLAQUENIL SO_4
Trade name for Hydroxychloroquine SO_4

PLASMOCHIN NAPHTHOATE (Winthrop)
Trade name for Pamaquine Naphthoate

PLASMOQUINE
Synonym for Pamaquine Naphthoate

PLAVOLEX (Wyeth)
Trade name for Dextran

PLAZMOID (Upjohn)
Trade name for Gelatin Solution Purified

PLECYAMIN 12 (Plessner)
Trade name for Cyanocobalamin

PM 396
Synonym for Methsuximide

PODOPHYLLIN
Administration Topical
Dosage form Ointment, 25%

POLARAMINE (Schering)
Trade name for Dextro-chlorpheniramine

POLOXALKOL
Trade name Polykol (Upjohn)
Administration Oral
Dosage form Liquid, 200 mg per ml

POLYAMINE METHYLENE RESIN
Trade names Exorbin (Ayerst), Resinat (National), Basex (Columbus)
Administration Oral
Dosage form Tablet 0 25 Gm

POLYBRENE (Abbott)
Trade name for Hexad methrine Br

POLYCYCLINE (Bristol)
Trade name for Tetracycline

POLYCYCLINE HCl (Bristol)
Trade name for Tetracycline HCl

POLYESTRADIOL PO_4
Trade name Estradurin (Ayerst)
Administration Intramuscular
Dosage form Vial, 40 mg

POLYETHYLENE GLYCOLS
Carbowax 400 Carbowax 1000, Carbowax 1500 Carbowax 1540 Carbowax 4000, (all Carbide and Carbon)

POLYKOL (Upjohn)
Trade name for Poloxalkol

POLYMYXIN B SO_4
Trade name Aerosporin (Burroughs Wellcome)
Administration Oral, intramuscular intrathecal topical
Dosage forms Vials 200,000 and 500 000 units tablet 500 000 units

POLYOXYETHYLENE 20
Synonym for Polysorbate 80

POLYSORB HYDRATE (Fougera)
Trade name for Sorbitan Sesquioleate Emulsion

POLYSORBATE 20
Synonyms Sorbitan Monolaurate, Tween 20 Emulsifier

POLYSORBATE 80
Synonyms Polyoxyethylene 20, Sorbitan Mono-oleate Tween 80
Trade names Monitan (Ives Cameron), Sorlate (Abbott)

POLYVINYLPYRROLIDONE
Trade name PVP Macrose (Schenley)
Administration Intravenous
Dosage form Bottle, 3 5%

PROCAINE BUTYRATE
Trade name Probutylin (Roter)
Administration Oral
Dosage forms Capsules, 0 3 Gm elixir, 100 mg per ml

PROCAINE HCl
Trade name Novocain (Winthrop)
Administration Parenteral
Dosage forms A variety of concentrations

PROCAINE PENICILLIN G
Trade names Abbocillin (Abbott), Com pen (C S C), Crysticillin (Squibb) Depo [illegible] lin (Wyeth)
Administration Oral parenteral
Dosage forms A wide variety of forms

PROCHLORPERAZINE DIMALEATE
Trade name Compazine (Smith, Kline & French)
Administration Oral, rectal, intramuscular
Dosage forms Tablets, 5 mg, 10 mg, 25 mg syrup suppositories, 5 mg, 25 mg, *ampule, 10 mg (as ethanedisulfonate)*

PROCHOLON (Squibb)
Trade name for Dehydrocholic Acid

PROCYCLIDINE HCl
Trade name Kemadrin (Burroughs Well come)
Administration Oral
Dosage form Tablet, 5 mg

PRODOX (Upjohn)
Trade name for Hydroxyprogesterone Acetate

PROGESTERONE
Trade names Colprosterone (Ayerst), Dela lutin (Squibb), Lipo Lutin (Parke, Davis), Lucorteum (Merck), Lutocylin (Ciba), *Lutromone (Endo), Migesterone (Durst)*, Progestin (Organon), Proluton (Schering), Syngesterone (Pfizer) and many others
Administration Intramuscular, *sublingual*, oral
Dosage forms Ampules, 10, 25 mg per ml in oil and aqueous suspension *tablets, 10, 25 mg*

PROGESTIN (Organon)
Trade name for Progesterone

PROGESTONE (Carnrick)
Trade name for Corpus Luteum

PROGESTORAL (Organon)
Trade name *for Ethisterone*

PROGUANIL HCl
Synonym for Chloroguanide HCl

PROGYNON (Schering)
Trade name for Estradiol

PROGYNON B (Schering)
Trade name for Estradiol Benzoate

PROGYNON DP (Schering)
Trade name for Estradiol Dipropionate

PROLACTIN
Trade name Luteotrophin (Squibb)
Administration Intramuscular and subcuta neous
Dosage form Ampule to be diluted to 40 units per ml

PROLAX (Cole)
Trade name for Mephenesin

PROLIXIN (Squibb)
Trade name for Fluphenazine Dihydrochlo ride

PROLOID (Warner Chilcott)
Trade name for Thyroglobulin

PROLUTON (Schering)
Trade name *for Progesterone*

PROLUTON C (Schering)
Trade name for Ethisterone

PROMACETIN *(Parke, Davis)*
Trade name for Acetosulfone

PROMAZINE HCl
Trade name Sparine (Wyeth)
Administration Oral intravenous, intramus cular
Dosage forms Tablets, 25 50 100 mg, vial, *50 mg per ml*

PROMETHAZINE HCl
Trade name Phenergan (Wyeth)
Administration Oral and topical
Dosage forms Tablet, 12 5 mg, syrup 1 25 mg per ml cream, 2%

PROMETHESTROL DIPROPIONATE
Trade name Meprane Dipropionate (Reed & Carnrick)
Administration Oral
Dosage form Tablet, 1 mg

PROMIN (Parke, Davis)
Trade name for Glucosulfone Sodium

PROMIZOLE (Parke, Davis)
Trade name for Thiazolsulfone

PRAMOXINE HCl
Trade name Tronothane (Abbott)
Administration Topical
Dosage forms Solution lotion cream 1%

PRANONE (Schering)
Trade name for Ethisterone

PRANTAL METHYLSULFATE (Schering)
Trade name for Diphemanil Methylsulfate

PREDNIS (Arlington)
Trade name for Prednisolone

PREDNISOLONE
Trade names Co-Hydeltra (Merck) Delta Cortef (Upjohn) Hydeltra (Merck) Meticortelone (Schering) Paracortol (Parke Davis) Prednis (Arlington) Sterane (Pfizer) Sterolone (Rowell)
Administration Oral topical
Dosage forms Tablet 5 mg spray 50 mg

PREDNISOLONE ACETATE
Trade name Sterane Intramuscular (Pfizer
Administration Intramuscular
Dosage form Vial 5 mg per ml

PREDNISOLONE BUTYLACETATE
Trade name Hydeltra T B A (Merck)
Administration Into tissue or joints
Dosage form Ampule 20 mg per ml

PREDNISOLONE 21 PO
Trade name Hydeltrasol (Merck)
Administration Topical
Dosage form Solution 0 5%

PREDNISOLONE SODIUM HEMISUCCINATE
Trade name Meticortelone Soluble (Schering)
Administration Intravenous intramuscular
Dosage form Vial 150 mg

PREDNISONE
Trade names Deltasone (Upjohn) Deltra (Merck) Meticorten (Schering) Paracort (Parke Davis)
Administration Oral
Dosage form Tablet 5 mg

PREGNENOLONE
Trade names Arthenolone (Ayerst) Enelone (Funk) Natolone (National) Prenolon (Schering) Sharmone (Merck)
Administration Oral intramuscular
Dosage forms Tablet 100 mg vial 100 mg per ml

PREGNYL (Organon)
Trade name for Chorionic Gonadotropin

PRELUDIN (Geigy)
Trade name for Phenmetrazine HCl

PREMARIN (Ayerst)
Trade name for Estrogenic Substances Conjugated

PREMOCEL (Premo)
Trade name for Methylcellulose

PREMODRIN (Premo)
Trade name for Methamphetamine HCl

PRENDEROL (Squibb)
Trade name for Diethyl Propanediol

PRENOLON (Schering)
Trade name for Pregnenolone

PRIMAQUINE PO
Administration Oral
Dosage form Tablet 15 mg as base

PRIMIDONE
Trade name Mysoline (Ayerst)
Administration Oral
Dosage form Tablet 0 25 Gm

PRIODAX (Schering)
Trade name for Iodoalphionic Acid

PRISCOLINE (Ciba)
Trade name for Tolazoline HCl

PRIVINE HCl (Ciba)
Trade name for Naphazoline HCl

PRO BANTHINE Br (Searle)
Trade name for Propantheline Br

PROBARBITAL CALCIUM
Trade name Ipral Calcium (Squibb)
Administration Oral
Dosage form Tablets 50 130 mg

PROBENECID
Trade name Benemid (Merck)
Administration Oral
Dosage form Tablet 0 5 Gm

PROBUTYLIN (Rorer)
Trade name for Procaine Butyrate

PROCAINE AMIDE
Trade name Pronestyl (Squibb)
Administration Oral intravenous
Dosage forms Capsule 0 25 Gm ampule 100 mg per ml

PROCAINE AMIDE HCl
Trade name Pronestyl HCl (Squibb)
Administration Oral intravenous
Dosage forms Capsule 0 25 Gm vial 100 mg per ml

PTEROYL TRIGLUTAMATE SODIUM
Trade name Teropterin (Lederle)
Administration Intramuscular, intravenous
Dosage form Ampule, 10 mg per ml

PUNICINE TANNATE (N.Y. Quinine)
Trade name for Pelletierine Tannate

PURINETHOL (Burroughs Wellcome)
Trade name for Mercaptopurine

PURODIGIN (Wyeth)
Trade name for Digitoxin

PVP-MACROSE (Schenley)
Trade name for Polyvinylpyrrolidone

PYDIRONE (Breon)
Preparation of Dipyrone

PYMAFED (Lloyd)
Trade name for Pyrilamine Maleate

PYOKTANIN (Merck)
Trade name for Methylrosaniline Cl

PYRA-MALEATE (VanPelt & Brown)
Trade name for Pyrilamine Maleate

PYRAMIDON (Winthrop)
Trade name for Aminopyrine

PYRATHIAZINE HCl
Trade name Pyrrolazote (Upjohn)
Administration Oral
Dosage forms Tablets, 25, 50, and 100 mg, elixir, 2.5 mg per ml

PYRAZINAMIDE (Merck)
Trade name for Pyrazinoic Acid Amide

PYRAZINOIC ACID AMIDE
Trade names Aldinamide (Lederle), Pyrazinamide (Merck)
Administration Oral
Dosage form Tablet, 0.5 Gm

PYRAZOLINE
Synonym for Antipyrine

PYRETHRUM
Administration Oral
Dosage forms Various forms

PYRIBENZAMINE (Ciba)
Trade name for Tripelennamine HCl

PYRICIDIN (Nepera)
Trade name for Isoniazid

PYRIDINE ALDOXIMINE METHIOD
Synonym PAM
Not available on commercial drug market

PYRIDIUM (Merck)
Trade name for Phenylazo-diamino pyri HCl

PYRIDOSTIGMIN Br
Trade name Mestinon Br (Roche)
Administration Oral
Dosage form Tablet, 60 mg

PYRIDOXINE HCl
Synonym Vitamin B_6
Trade names Beadox (Premo), Hexa Bet (Lilly), Hexavibex (Parke, Davis)
Administration Oral, intravenous
Dosage forms Tablets, 10, 25, 50 mg, s tions, 25, 50, 100 mg per ml

PYRILAMINE MALEATE
Trade names Antihist (Lipton), Diamu (Merck), Copsamine (Durst), Hist (Sherman), Neo-Antergan (Merck), P minyl (Buffington), Pymafed (Lloy Pyra Maleate (VanPelt & Brown), R stamin (Strasenburgh), Stangen (Ph cians Drug), Statomin (Bowman), Th gen (Rorer), and many others
Administration Oral
Dosage forms Various forms

PYRIMETHAMINE
Trade name Daraprim (Burroughs W come)
Administration Oral
Dosage form Tablet, 25 mg

PYROGALLIC ACID
Synonym Pyrogallol
Dosage form Ointment, 2 to 10%

PYROGALLOL
Synonym for Pyrogallic Acid

PYRONIL (Lilly)
Trade name for Pyrrobutamine PO_4

PYRROBUTAMINE PO_4
Trade name Pyronil (Lilly)
Administration Oral
Dosage form Tablet, 15 mg

PYRROLAZOTE (Upjohn)
Trade name for Pyrathiazine HCl

PYRVINIUM Cl
Trade names Poquil (Parke, Davis), Va quin (Parke, Davis)
Administration Oral
Dosage form Suspension, 5 mg per ml

PROMOXOLANE
Trade name Dimethylane (National)
Administration Oral
Dosage form Capsule, 0 25 Gm

PRONESTYL (Squibb)
Trade name for Procaine Amide

PRONESTYL HCl (Squibb)
Trade name for Procaine Amide HCl

PROPADRINE HCl (Merck)
Trade name for Phenylpropanolamine HCl

PROPANTHELINE Br
Trade name Pro-Banthine Br (Searle)
Administration Oral intravenous intramuscular
Dosage form Tablet, 15 mg ampule 30 mg

PROPARACAINE HCl
Trade name Ophthaine (Squibb)
Administration Topical
Dosage form Solution 5 mg per ml

PROPASA (Merck)
Trade name for Aminosalicylic Acid

PROPHENPYRIDAMINE MALEATE
Synonym for Pheniramine Maleate

PROPIODAL
Trade name Entodon (Winthrop)
Administration Parenteral
Dosage form Ampule 118 mg Iodine per ml

PROPION GEL (Wyeth)
Trade name for Propionate Compound

PROPIONATE CAPRYLATE COMPOUND
Trade name Sopronol (Wyeth)
Dosage forms Ointment 30% powder and solution 25%

PROPIONATE COMPOUND
Trade name Propion Gel (Wyeth)
Administration Topical
Dosage form Gel 20%

PROPOXYCAINE HCl
Trade name Blockain (Breon)
Administration Parenteral
Dosage form Ampule 5 mg per ml

PROPYLHEXEDRINE
Trade name Benzedrex
Administration Inhalation
Dosage form Inhaler 250 mg

PROPYLIODINE
Trade name Dionosil (Glaxo)
Administration Intrabronchial
Dosage forms Vials aqueous suspension (50%) with sodium carboxymethylcellulose oily suspension (60%)

PROPYLTHIOURACIL
Administration Oral
Dosage form Tablets, 25 and 50 mg

PROSCOMIDE (Miller)
Trade name for Methscopolamine Br

PROSTIGMIN Br (Roche)
Trade name for Neostigmine Br

PROSTIGMIN METHYLSULFATE (Roche)
Trade name for Neostigmine Methylsulfate

PROTAMINE SO
Administration Intravenous
Dosage form Ampule 10 mg per ml

PROTAMINE ZINC AND ILETIN (Lilly)
Trade name for Protamine Zinc Insulin

PROTAMINE ZINC INSULIN
Synonym PZI
Trade name Protamine Zinc and Iletin (Lilly)
Administration Subcutaneous
Dosage form Vials 40 and 80 units per ml

PROTHYRIN
Trade name Thyractin (Winthrop)
Administration Oral
Dosage form Tablet 25 mg

PROTOVERATRINES A AND B
Trade names Provell (Lilly) Veralba (Pitman Moore) and others especially in mixtures
Administration Oral intramuscular intravenous
Dosage forms Tablets 0 2 and 0 5 mg vial 0 2 mg per ml

PROVELL (Lilly)
Trade name for Protoveratrines A and B

PROVITAMIN A
Synonym for Carotene

PSEUDOEPHEDRINE HCl
Synonym for Isoephedrine HCl

PSEUDOMONAS POLYSACCHARIDES
Trade name Piromen (Travenol)
Administration Intramuscular
Dosage form Vial, 4 and 10 mcg per ml

P S P
Synonym for Phenolsulfonphthalein

PSYLLIUM
Trade names Metamucil (Searle) Mucilose (Winthrop) Serutan (Pharm Inc)
Administration Oral
Dosage forms As such or with dextrose

RAPHETAMINE PO₄ (Strasenburgh)
Trade name for Amphetamine PO₄

RASPBERIN (Miller)
Trade name for Salicylamide

RAUDIXIN (Squibb)
Trade name for *Rauwolfia serpentina*

RAUREN (Maney)
Trade name for Reserpine

RAURINE (Lloyd)
Trade name for Reserpine

RAU-SED (Squibb)
Trade name for Reserpine

RAU-TAB (National)
Trade name for Alseroxylon

RAUTENSIN (Smith-Dorsey)
Trade name for Alseroxylon

RAUWILOID (Riker)
Trade name for Alseroxylon

RAUWISTAN (Thompson)
Trade name for *Rauwolfia serpentina*

RAUWOLFIA SERPENTINA
Trade names [illegible]

[illegible]

RED BLOOD CELLS, HUMAN DRIED
Trade name Lyocyte (Merck)
Administration Topical
Dosage form Powder, as such

REDISOL (Merck)
Trade name for Cyanocobalamin

REGITINE HCl (Ciba)
Trade name for Phentolamine HCl

REGITINE METHANESULFONATE (Ciba)
Trade name for Phentolamine Methanesulfonate

REGUTOL (Pharmaco)
Trade name for Dioctyl Sodium Sulfosuccinate

RELA (Schering)
Trade name for Carisoprodol

RELAXIN
Trade names Cervilaxin (National), Releasin (Warner Chilcott)
Administration Parenteral
Dosage form Ampule, 20 mg per ml

RELEASIN (Warner-Chilcott)
Trade name for Relaxin

RENCAL (Squibb)
Trade name for Sodium Phytate

RENNIN
Administration Oral
Dosage form As such

RENOGRAFIN (Squibb)
Trade name for Diatrizoates, Sodium and Methylglucamine

RENSTAMIN (Strasenburgh)
Trade name for Pyrilamine Maleate

RESCINNAMINE
Trade name Moderil (Pfizer)
Administration Oral
Dosage form Tablets, 0 25 and 0 5 mg

RESERCEN (Central)
Trade name for Reserpine

RESERPINE
Trade names Crystoserpine (Smith Dorsey), Eskaserp (Smith, Kline & French), Key-Serpine (Key), Rauren (Maney), Raurine (Lloyd), Rau-Sed (Squibb), Resercen (Central), Reserpoid (Upjohn), Roxinoid (Merck), Sandril (Lilly), Serfin (Parke, Davis), Serpanray (Panray), Serpasil [illegible] (Riker), [illegible] (Vita [illegible]hers
[illegible] s, 0 1 [illegible] per ml

RESERPOID (Upjohn)
Trade name for Reserpine

RESIN CAPRYLATE
Trade name Kaprylex (Strasenburgh)
Administration Oral
Dosage form Capsule, 250 mg

RESINAT (National)
Trade name for Polyamine Methylene Resin

RESISTAB (Bristol-Meyers)
Trade name for Thonzylamine HCl

RESODEC (Smith, Kline & French)
Trade name for Carboxylic Resin

RESORCIN
Synonym for Resorcinol

RESORCINOL
Administration Topical
Dosage forms Various forms

PYRVINIUM PAMOATE
Trade name Povan (Parke Davis)
Administration Oral
Dosage form Suspension 10 mg base per ml

PZA
Synonym for Pyrazinamide

PZI
Synonym for Protamine Zinc Insulin

QUADRINAL (Bilhuber Knoll)
Each tablet contains Ephedrine HCl 25 mg Phenobarbital 25 mg Theophylline calcium Salicylate 0 13 Gm Potassium Iodide 0 3 Gm

QUADRI SULFA MIXTURE
Trade name Deltamide (Armour)
Administration Oral
Dosage forms Tablet 0 5 Gm fluid 100 mg per ml
Remarks Mixture of Sulfadiazine Sulfamerazine Sulfamethazine, Sulfacetamide

QUASSIA
Administration Oral
Dosage form As such

QUELICIN Cl (Abbott)
Trade name for Succinylcholine Cl

QUERCETIN
Trade name Quertine (Abbott)
Administration Oral
Dosage form Tablets 10 and 20 mg

QUERTINE (Abbott)
Trade name for Quercetin

QUIACTIN (Merrell)
Trade name for Oxanamide

QUINACRINE HCl
Synonym Mepacrine
Trade name Atabrine HCl (Winthrop)
Administration Oral
Dosage form Tablet, 100 mg

QUINAGLUTE (Wynn)
Trade name for Quinidine Gluconate

QUINICARDINE (Varick)
Trade name for Quinidine SO_4

QUINIDINE GLUCONATE
Trade name Quinaglute (Wynn)
Administration Oral intramuscular
Dosage forms Tablet, 325 mg ampule 80 mg per ml

QUINIDINE HCl
Administration Intramuscular
Dosage form Ampule, 5 ml containing 0 6 Gm

QUINIDINE SO_4
Trade name Quinicardine (Varick)
Administration Oral intramuscular
Dosage forms Tablets capsules, 0 1 and 0 2 Gm ampules containing 0 2 mg dissolved in Propylene Glycol

QUININE
Administration Oral
Dosage forms Various forms

QUININE AND UREA HCl
Administration Intravenous
Dosage form Ampule, 50 mg per ml

QUININE DIHYDROCHLORIDE
Administration Intravenous intramuscular
Dosage forms Ampules of varying size

QUININE ETHYLCARBONATE
Synonym Euquinine
Administration Oral
Dosage forms A variety of forms

QUINOXYL (Burroughs Wellcome)
Trade name for Chiniofon

QUOTANE HCl (Smith Kline & French)
Trade name for D methisoquin HCl

RABELLON (Merck)
Trade name for mixture containing Hyoscyamine HBr 0 45 mg Atropine SO_4, 0 04 mg Scopolamine HBr 0 01 mg per tablet

RACEPHEDRINE HCl
Synonym Ephedrine HCl

RACHOMATE (Abbott)
Trade name for Sodium Radio Chromate

RADIOACTIVE THORIUM
Trade name Thorium X (Fleischman Burd)
Dosage forms Ointment alcohol lacquer

RADIO GOLD COLLOID
Synonym Au^{198} Aurcoloid
Administration Intravenous
Dosage forms Solutions, 20 40 millicuries per ml

RADIO IODINATED SERUM ALBUMIN (HUMAN)
Trade name Risa (Abbott)
Administration Intravenous
Dosage form Vials 1 or more millicuries

RADIO IODINE^{131}
Synonym I^{131}
Not available on the commercial drug market

RAPACODIN (Bilhuber Knoll)
Trade name for Dihydrocodeine Bitartrate

SALETHYL CARBONATE (Parke, Davis)
Trade name for Carbethyl Salicylate

SALICIM (Irwin Neisler)
Trade name for Salicylamide

SALICYLAMIDE
Trade names Amid Sal (Glenwood), Liquiprin (Johnson & Johnson), Raspberin (Miller) Salamide (Columbus), Salicim (Irwin Neisler) Salrin (Warren Teed)
Administration Oral
Dosage form Tablets 0 3 and 0 6 Gm

SALICYLANILIDE
Trade names Ansadol (Rorer), Salinidol (Doak)
Administration Topical
Dosage form Ointment 4 5%

SALICYLAZOSULFAPYRIDINE
Trade name Azulfidine (Pharmacia)
Administration Oral
Dosage form Tablet 0 5 Gm

SALICYLIC ACID
Administration Topical
Dosage forms Various forms

SALICYLOPHENYLFORMIC ACID
Trade name Merythrol (Chemico)
Administration Topical
Dosage forms Solution, 0 1, 0 04% tincture, 0 033%

SALINE NORMAL
Synonym for Sodium Cl Solution Isotonic

SALINIDOL (Doak)
Trade name for Salicylanilide

SALOPHEN (Winthrop)
Trade name for Phenetsal

SALRIN (Warren Teed)
Trade name for Salicylamide

SALUNDEK (Wallace & Tiernan)
Trade name for Zinchlorundesal

SALURON (Bristol)
Trade name for Hydroflumethiazide

SALYRGAN THEOPHYLLINE (Winthrop)
Trade name for Mersalyl and Theophylline

SANDOPTAL (Sandoz)
Trade name for Allylbarbital

SANDRIL (Lilly)
Trade name for Reserpine

SANTONIN
Administration Oral
Dosage form As such

SASS (Abbott)
Trade name for Cholesterol Lowering Factor

SCARLET RED
Administration Topical
Dosage form Ointment 5%

SCILLAREN (Sandoz)
Administration Oral
Dosage forms Tablet 0 8 mg solution 0 8 mg per ml

SCILLAREN B (Sandoz)
Administration Intravenous
Dosage form Ampules 0 5 mg in 1 ml

SCOPOLAMINE
Synonym Hyoscine
Administration Oral subcutaneous intravenous
Dosage form A variety of forms

SCOPOLAMINE HBr
Synonym Hyoscine HBr
Administration Oral subcutaneous
Dosage forms Tablets 0 3 and 0 6 mg ampules 0 4 and 0 65 mg per ml

SCOPOLAMINE METHYLBROMIDE
Synonym for Methscopolamine Br

SEBIZON (Schering)
Proprietary lotion containing Sulfacetamide

SECOBARBITAL SODIUM
Trade name Evronal Sodium (Evron) Seconal Sodium (Lilly)
Administration Oral rectal intravenous
Dosage forms Capsules, tablets 30 50 100 mg suppositories 65 130, 200 mg ampules 0 25 0 5 Gm to be diluted

SECONAL SODIUM (Lilly)
Trade name for Secobarbital Sodium

SEDAMYL (Schenley)
Trade name for Acetylbromdiethylacetylcarbamid

SEDULON (Roche)
Trade name for Dihyprylone

SELSUN SULFIDE SUSPENSION (Abbott)
Selenium Sulfide shampoo

SEMIKON (Massengill)
Trade name for Methapyrilene HCl

SEMILENTE ILETIN (Lilly)
Trade name for Semilente Insulin

RESORCINOL MONOACETATE
Trade name Euresol (Bilhuber Knoll)
Administration Topical
Dosage forms Various forms

RESTROL (Central)
Trade name for Dienestrol

RETICULOGEN (Lilly)
Trade name for Liver Injection Purified Contains small amount of Thiamine Cl

RETROGRAFIN (Squibb)
Trade name for Sodium and Methylglucamine Diatrizoate with Neomycin

REXAURUM (Kahlenberg)
Trade name for Colloidal Gold

R GENE (Cutter)
Trade name for l Arginine HCl

RHUBARB
Administration Oral
Dosage form Extract

RIASOL (Shield)
Phenol mercury soap

RIBOFLAVIN
Synonyms Lactoflavin Vitamin B_2 Vitamin G
Trade name Flavaxin (Winthrop)
Administration Oral parenteral
Dosage forms Tablets 1 5 and 10 mg ampule 5 mg

RIBOFLAVIN METHYLOL
Trade name Hyflavin (Endo)
Administration Intravenous intramuscular
Dosage form Vials 10 mg per ml

RICINOLEIC ACID
Trade name Aci Jel (Ortho)
Administration Topical
Dosage form Gel

RIMIFON (Roche)
Trade name for Isoniazid

RINGER S SOLUTION
Synonym Isotonic Solution of Three Chlorides
Administration Intravenous subcutaneous
Dosage form Bottles as such

RIOGON (Breon)
Trade name for Chorionic Gonadotropin

RISA (Abbott)
Trade name for Radio Iodinated Serum Albumin (Human)

RISTOCETIN
Trade name Spontin (Abbott)
Administration Intravenous
Dosage form Vial 500 mg

RITALIN HCl (Ciba)
Trade name for Methylphenidate HCl

ROBALATE (Robins)
Trade name for Dihydroxy Aluminum Aminoacetate

ROBAXIN (Robins)
Trade name for Methocarbamol

ROBITUSSIN (Robins)
Trade name for Glyceryl Guaiacolate

ROCCAL (Winthrop)
Trade name for Benzalkonium Cl

ROLICTON (Searle)
Trade name for Amisometradine

ROMILAR HBr (Roche)
Trade name for Dextromethorphan HBr

RONIACOL (Roche)
Trade name for Beta pyridyl-carbinol

ROSE BENGAL
Not readily available on commercial drug market

ROTENONE
Administration Topical
Dosage forms Various forms and concentrations are available

ROXINOID (Merck)
Trade name for Reserpine

RUBRAMIN (Squibb)
Trade name for Cyanocobalamin

RUTIN
Synonym Vitamin P Factor
Administration Oral
Dosage form Tablets 20 50 60 100 mg

SAFF (Abbott)
Trade name for Safflower Oil

SAFFLOWER OIL
Trade name Saff (Abbott)
Administration Oral
Dosage form Emulsion

SAF TAN (Texas Pharmacal)
Trade name for Digallol Trioleate Liquid

SALAMIDE (Columbus)
Trade name for Salicylamide

SINTROM (Geigy)
Trade name for Acenocoumarol

SITOSTEROLS
Trade name Cytellin (Lilly)
Administration Oral
Dosage form Suspension, 20%

SKIN FILM (Dome)
Water soluble barrier to irritant oils

SKIODAN SODIUM (Winthrop)
Trade name for Methiodal Sodium

SKOLEX (Williams)
Propylene Glycol and Para aminobenzoic acid liquid

SKOPOLATE (Strasenburgh)
Trade name for Methscopolamine NO,

SLEEP EZE
Trade name for Methapyrilene

SODIUM ACETRIZOATE
Trade names Thixokon (Mallinckrodt), Urokon Sodium (Mallinckrodt)
Administration Intravenous
Dosage form Ampules, 30%, 50%

SODIUM p-AMINOHIPPURATE
Administration Intravenous
Dosage form Ampule, 200 mg per ml

SODIUM AMINOPTEROYLGLUTAMATE
Trade name Aminopterin Sodium (Lederle)
Administration Oral
Dosage form Tablet, 0 5 mg

SODIUM AMINOSALICYLATE
Synonym Sodium Para aminosalicylate
Trade names Pamisyl Sodium (Parke, Davis), Pasara Sodium (Smith Dorsey), Pasem Sodium (Massengill), Parasal Sodium (Panray)
Administration Oral
Dosage form Tablet 0 5 Gm

SODIUM AND CALCIUM ALGINATE
Trade name Kalpin (Wallace)
Administration Oral
Dosage form As such

SODIUM AND METHYLGLUCAMINE DIACETYLAMINOTRIIODOBENZOATES
Trade name Gastrografin (Squibb)
Administration Oral
Dosage form Solution, 76%

SODIUM AND METHYLGLUCAMINE DIATRIZOATES WITH NEOMYCIN
Trade name Retrografin (Squibb)
Administration Intra ureteral
Dosage form 300 mg per ml wi 25 mg per ml Neomycin

SODIUM AND POTASSIUM GLUTAMATES
Trade name Glutavene K (Gray)
Administration Intravenous
Dosage form Vial, 25%

SODIUM BENZOATE
Administration Intravenous
Dosage form Ampule, 88 5 mg per ml

SODIUM BICARBONATE
Administration Oral, intravenous
Dosage forms Tablets of various sizes am pules, isotonic (1 3%), hypertonic (7 5%)

SODIUM BIPHOSPHATE
Synonym Sodium PO, Acid
Administration Oral
Dosage form Tablet, 0 3 Gm

SODIUM BISMUTH THIOGLYCOLLATE
Trade name Thio-Bismol (Parke, Davis)
Administration Intramuscular
Dosage form Ampule, 0 2 Gm

SODIUM CACODYLATE
Administration Subcutaneous, intravenous intramuscular
Dosage form Ampules, 0 05, 0 065, 0 1, 0 13 0 2, 0 25, and 0 5 Gm per ml

SODIUM CAPRYLATE
Administration Topical
Dosage forms As such, solution 20%

SODIUM CITRATE
Administration Oral
Dosage form Powder

SODIUM Cl SOLUTION, HYPERTONIC
Administration Intravenous
Dosage form Ampules, 2 to 5%

SODIUM Cl SOLUTION, HYPOTONIC
Administration Intravenous
Dosage form Ampule, 0 425% in 2 5% Dextrose

SODIUM Cl SOLUTION, ISOTONIC
Synonym Normal saline
Administration Intravenous
Dosage form Bottles of various sizes

SODIUM DEHYDROCHOLATE
Trade names Decholin Sodium (Ames), Dilabil Sodium (Breon)
Administration Intravenous
Dosage form Ampule, 200 mg per ml

SODIUM DIPROPIONAMIDO TRIIODO

xlt)
Intra-arterial
30 ml
50 ml

SEMILENTE INSULIN
Trade name Semi Lente Iletin (Lilly)
Administration Subcutaneous
Dosage forms Vials 40 U per ml 80 U per ml

SEMOXYDRINE (Massengill)
Trade name for Methamphetamine HCl

SENNA
Trade name Senokot (Purdue)
Administration Oral
Dosage forms Tablet 225 mg as such

SENNOSIDES A AND B
Trade name Glysennid (Sandoz)
Administration Oral
Dosage form Tablet 12 mg

SENOKOT (Purdue)
Trade name for Senna

SEREMIUM (Squibb)
Trade name for Ethoxazene

SERFIN (Parke Davis)
Trade name for Reserpine

SEROMYCIN (Lilly)
Trade name for Cycloserine

SERPANRAY (Panray)
Trade name for Reserpine

SERPASIL (Ciba)
Trade name for Reserpine

SERPATE (Vale)
Trade name for Reserpine

SERPILOID (Riker)
Trade name for Reserpine

SERPINE (Pitman Moore)
Trade name for Reserpine

SERPIVITE (Vitarine)
Trade name for Reserpine

SERFOID (Canfield)
Trade name for Reserpine

SERUTAN (Pharm Inc)
Trade name for Psyllium

SERYNL
Synonym for Azaserine

SHARMONE (Merck)
Trade name for Pregnenolone

SIGMAMYCIN (Pfizer)
Trade name for mixture of Tetracycline and Oleandomycin PO.

SIGNEMYCIN V (Pfizer)
Trade name for mixture of Tetracycline PO, buffered and Oleandomycin PO.

SILICONE PROTECTIVE CREAMS
Covicone (Abbott) Domicone (Dome), Silicote (Arnar Stone)

SILICOTE (Arnar-Stone)
Silicone protective cream

SILVER Cl COLLOIDAL
Trade name Lunosol (Hille)
Dosage forms Solution 10% ointment 10%

SILVER I COLLOIDAL
Trade name Neo Silvol (Parke Davis)
Dosage forms Capsules approximately 0 4 Gm solutions and suppositories

SILVER NO_3
Synonym Lunar Caustic
Dosage form As such fused sticks

SILVER PICRATE
Trade name Picragol (Wyeth)
Administration Intravaginal
Dosage forms Powder 50 mg suppositories 0 065 and 0 13 Gm

SILVER POTASSIUM CYANIDE POTASSIUM CHOLEATE
Trade name Silvogon (Bischoff)
Administration Topical
Dosage forms As such tablet 26 mg

SILVER PROTEIN, MILD
Trade names Argyrol (Barnes), Lunargen (Lilly) Silvol (Parke, Davis)
Administration Topical
Dosage forms Many forms

SILVOGON (Bischoff)
Trade name for Silver Potassium Cyanide Potassium Choleate

SILVOL (Parke Davis)
Trade name for Silver Protein Mild

SINAN (Warren Teed)
Trade name for Mephenesin

SINAXAR (Armour)
Trade name for Styramate

SINGOSERP (Ciba)
Trade name for Syrosingopine

SINOGRAFIN (Squibb)
A mixture of Renografin (Squibb) and Cholografin (Squibb)

SODIUM SO,
Synonym Glauber s Salt
Administration Oral
Dosage forms Crystals effervescent salts

SODIUM SUCCINATE
Synonym Sodium Succinate Hexahydrate
Trade name Soduxin (Brewer)
Administration Intravenous
Dosage form Ampule, 2 ml, 300 mg per ml

SODIUM TETRADECYL SO
Trade name Sotradecol Sodium (Wallace & Tiernan)
Administration Intravenous
Dosage form Vials, 1, 3, and 5%

SODIUM THIOSULFATE
Synonym Sodium Hyposulfite, Hypo
Administration Intravenous
Dosage form Ampules 0 5 to 1 0 Gm

SODIUM VERSENATE (Riker)
Trade name for Edathamil Disodium

SODUXIN (Brewer)
Trade name for Sodium Succinate

SOFTRAN (Stuart)
Trade name for Buclizine HCl

SOLACTHYL (Squibb)
Trade name for Corticotropin

SOLAR CREAM (Doak)
Para aminobenzoic acid and Titanium Dioxide cream

SOLESTRO (Merck)
Trade name for Estradiol Benzoate

SOLGANAL (Schering)
Trade name for Aurothioglucose

SOLUBLE LIVER FRACTION
Synonym for Liver Fraction 1

SOLU CORTEF (Upjohn)
Trade name for Hydrocortisone Succinate

SOLUTHRICIN (Merck)
Trade name for Tyrothricin

SOLU ZYME (Upjohn)
Trade name for Vitamin B Complex

SOMA (Wallace)
Trade name for Carisoprodol

SOMATOTROPIN
Synonym for Chorionic Gonadotropin

SOMBULEX (Schenley)
Trade name for Methyl Cyclohexenyl Methyl barbituric Acid

SOMNALERT (Warren Teed)
Trade name for Hexobarbital

SOMNICAPS (Am Pharm)
Trade name for Methapyrilene HCl

SOMNOS (Merck)
Trade name for Chloral Hydrate

SOPRONOL (Wyeth)
Trade name for Propionate Caprylate Compound

SORBITAN MONOLAURATE
Synonym for Polysorbate 20

SORBITAN MONO OLEATE
Synonym for Polysorbate 80

SORBITAN SESQUIOLEATE
Trade name Polysorb Hydrate (Fougera)

SORICIN (Merrell)
Trade name for Sodium Ricinoleate

SORLATE (Abbott)
Trade name for Polysorbate 80

SOTRADECOL SODIUM (Wallace & Tiernan)
Trade name for Sodium Tetradecyl SO

SOYALOID (Dome)
Trade name for Colloids of Soya Beans

SPARINE (Wyeth)
Trade name for Promazine HCl

SPIRODON (Cutter)
Trade name for Tetrantoin

SPONTIN (Abbott)
Trade name for Ristocetin

STABISOL (Squibb)
Trade name for Bismuth Subsalicylate

STANGEN (Physicians Drug)
Trade name for Pyrilamine Maleate

STANOLONE
Trade name Adrolone (National)
Administration Intramuscular
Dosage form Vial 50 mg per ml

STATICIN (Merck)
Trade name for Caronamide

SODIUM GENTISATE
Trade name Na Gent (Raymer)
Administration Oral
Dosage form Tablet, 0 3 Gm

SODIUM GLUTAMATE
Trade name Glutavene (Gray)
Administration Intravenous
Dosage form Vial, 25%

SODIUM HYPOSULFITE
Synonym for Sodium Thiosulfate

SODIUM INDIGOTINDISULFONATE
Synonym Indigo Carmine
Administration Intravenous, intramuscular, and subcutaneous
Dosage form Ampule 8 mg per ml

SODIUM I
Administration Intravenous
Dosage form Ampules of various sizes

SODIUM IODOMETHAMATE
Trade name Neo-Iopax (Schering)
Administration Intravenous and retrograde
Dosage forms Solutions, 50 and 75%

SODIUM LACTATE
Administration Intravenous, subcutaneous
Dosage form Bottles, 1/6 molar and molar to be diluted

SODIUM LAURYL SO_4
Trade name Neutrazyme (Smith Dorsey)
Administration Rectal
Dosage form Suppository, 100 mg

SODIUM LEVOTHYROXINE
Trade name Synthroid Sodium (Travenol)
Administration Oral
Dosage form Tablets, 0 1 and 0 2 mg

SODIUM LIOTHYRONINE
Synonym for Liothyronine Sodium

SODIUM MORRHUATE
Trade name Morusul (Endo)
Administration Intravenous
Dosage form Vial, 5% with Sulfadiazine

SODIUM NITRITE
Administration Intravenous
Dosage form Tablet or powder

SODIUM PARA AMINOBENZOATE
Synonym PABA Sodium
Administration Oral
Dosage form Tablet, 0 5 Gm

SODIUM PARA-AMINOSALICYLATE
Synonym for Sodium Aminosalicylate

SODIUM PENICILLIN
Available in troches for topical use

SODIUM PENICILLIN G
Administration Parenteral, topical
Dosage forms A variety of forms

SODIUM PERBORATE
Dosage form As such

SODIUM PEROXIDE
Dosage form As such

SODIUM PHYTATE
Trade name Rencal (Squibb)
Administration Rectal
Not on commercial drug market

SODIUM PO_4
Trade name Clyserol (Clyserol), Fleet Enema (Fleet), Travad (Travenol)
Administration Oral rectal
Dosage forms As such, and 20% solutions

SODIUM PO_4, ACID
Synonym for Sodium Biphosphate

SODIUM POLYSTYRENE SULFONATE
Trade name Kayexalate (Winthrop)
Administration Oral
Dosage form Powder, as such

SODIUM PSYLLIATE
Trade name Sylnasol (Searle)
Administration Intravenous
Dosage form Ampule, 5%

SODIUM RADIO CHROMATE
Trade name Rachomate (Abbott)
Administration Intravenous
Dosage form Solution which is mixed with blood before injection

SODIUM RADIO IODIDE
Synonym I^{131}
Administration Oral intravenous
Dosage forms Capsules, solution

SODIUM RADIO PHOSPHATE
Synonym P^{32}
Administration Oral, intravenous
Dosage form Solution

SODIUM RICINOLEATE
Trade name Soricin (Merrell)
Administration Intravenous
Dosage form Ampule, 2% solution

SODIUM SALICYLATE
Administration Oral
Dosage form Tablet, 0 3 Gm usually enteric-coated

STRYCIN (Squibb)
Trade name for Streptomycin SO

STYPTICIN (Merck)
Trade name for Cotarnine Cl

STYPVEN (Burroughs Wellcome)
Trade name for Venom, Russell Viper

STYRAMATE
Trade name Sinaxar (Armour)
Administration Oral
Dosage form Tablet, 200 mg

STYRONATE RESINS
Trade name Katonium (Winthrop)
Administration Oral
Dosage form Powder, 15 Gm

SUAVITIL (Merck)
Trade name for Benactyzine HCl

SUCARYL CALCIUM (Abbott)
Trade name for Cyclamate Calcium

SUCARYL SODIUM (Abbott)
Trade name for Cylcamate Sodium

SUCCINYLCHOLINE Cl
Trade names Anectine Cl (Burroughs Wellcome), Quelicin Cl (Abbott), Sucostrin (Squibb), Suxinyl (Fougera)
Administration Intravenous
Dosage form Solutions, 20, 50 mg per ml

SUCCINYLSULFATHIAZOLE
Trade name Sulfasuxidine (Merck)
Administration Oral
Dosage form Tablet, 0 5 Gm

SUCOSTRIN Cl (Squibb)
Trade name for Succinylcholine Cl

SUCRAPHEN (Smith Dorsey)
Trade name for Phenylephrine HCl

SUCROSE DEHYDRATING AGENT
Administration Intravenous
Dosage form Ampule 0 5 Gm per ml

SUDAFED (Burroughs Wellcome)
Trade name for Isoephedrine HCl

SUGRACILLIN (Upjohn)
Trade name for Potassium Penicillin G

SULAMYD (Schering)
Trade name for Sulfacetamide

SULAMYD SODIUM (Schering)
Trade name for Sulfacetamide Sodium

SULFSTREX PIPERAZINE (Abbott)
Trade name for Piperazine Estrone SO

SULFACETAMIDE
Trade names Sulamyd (Schering), Urosulfon (C M C)
Administration Oral
Dosage form Tablet, 0 5 Gm

SULFACETAMIDE SODIUM
Trade names Sebizon (Schering), Sulamyd Sodium (Schering)
Administration Topical
Dosage forms Ointments, 10%, solution 30%

SULFACETAMIDE-SULFADIAZINE SULFAMERAZINE MIXTURE
Synonym for Acet Dia Mer Sulfonamides

SULFADIAZINE
Trade names Cremodiazine (Merck), Lipo Diazine (Donley Evans)
Administration Oral
Dosage form Tablet 0 5 Gm

SULFADIAZINE SODIUM
Administration Intravenous
Dosage form Solution 50 mg per ml

SULFADIAZINE-SULFAMERAZINE MIXTURE
Synonym for Dia Mer Sulfonamides

SULFADIMER (Pitman Moore)
Trade name for Dia Mer Sulfonamides

SULFADIMETHOXINE
Trade names Madribon (Roche) Madriqid (Roche)
Administration Oral
Dosage forms Tablet 0 5 Gm , capsule, 125 mg , suspension 125 mg per ml

SULFAETHIDOLE
Trade name Sul Spansion (Smith Kline & French)
Administration Oral
Dosage forms Tablet 0 5 Gm sustained release tablet 650 mg suspension 130 mg per ml

SULFAGUANIDINE
Administration Oral
Dosage form Tablet 0 5 Gm

SULFAMERAZINE
Administration Oral
Dosage form Tablet 0 5 Gm

SULFAMERAZINE SODIUM
Administration Intravenous
Dosage form Solution 50 mg per ml

STATOMIN (Bowman)
Trade name for Pyrilamine Maleate

STEARODINE (Parke Davis)
Trade name for Calcium Iodostearate

STECLIN (Squibb)
Trade name for Tetracycline HCl

STELAZINE (Smith Kline & French)
Trade name for Trifluoperazine

STENEDIOL (Organon)
Trade name for Methandriol

STERANE (Pfizer)
Trade name for Prednisolone

STERANE INTRAMUSCULAR (Pfizer)
Trade name for Prednisolone Acetate

STERAQ (Ascher)
Trade name for Desoxycorticosterone Acetate

STERISIL (Warner Chilcott)
Trade name for Hexetidine

STEROLONE (Rowell)
Trade name for Prednisolone

STEROSAN (Geigy)
Trade name for Chlorquinaldol

STIBAMINE GLUCOSIDE
Trade name Neostam (Burroughs Wellcome)
Administration Intramuscular intravenous
Dosage form Ampule 1 Gm

STIBOPHEN
Synonym Neoantimosan
Trade name Fuadin (Winthrop)
Administration Intramuscular
Dosage form Ampule 8 5 mg as Antimony per ml

STIGMONENE Br (Warner Chilcott)
Trade name for Benzpyrinium Br

STILBAMIDINE ISETHIONATE
Administration Intravenous
Dosage form Ampule 150 mg

STILBESTROL
Synonym for Diethylstilbestrol

STILBETIN (Squibb)
Trade name for Diethylstilbestrol

STILPALMITATE (Abbott)
Trade name for Diethylstilbestrol Dipalmitate

STILPHOSTROL (Ames)
Trade name for Diethylstilbestrol Diphosphate

STIPOLAC (Burroughs Wellcome)
Trade name for Iodophthalein Sodium

STOMACH POWDERED
Trade name Ventriculin (Parke Davis)
Administration Oral
Dosage form As such

STRAMONIUM
Administration Oral
Dosage forms Capsules extracts tincture fluidextracts

STREPTODUOCIN
Trade names Combistrep (Pfizer) Distreptocin SO_4 (Lilly), Distrycin (Squibb), Duo Strep (Merck)
Equal parts of Streptomycin and Dihydrostreptomycin Sulfates
Administration Intramuscular
Dosage form Ampules 1 and 5 Gm

STREPTOKINASE STREPTODORNASE
Trade name Varidase (Lederle)
Administration Topical
Dosage form Vial 100 000 units Streptokinase 25 000 units Streptodornase

STREPTOMYCIN CALCIUM Cl
Administration Intramuscular
Dosage form Vials 1 and 5 Gm for dilution

STREPTOMYCIN SO_4
Trade name Strycin (Squibb)
Administration Intramuscular
Dosage form Vials equivalent of 1 0 and 5 0 Gm base

STRONG IODINE SOLUTION
Synonym Lugol s Solution
Administration Oral
Dosage form Diluted

STRONTIUM LACTATE
Trade name Strontolac (Wyeth)
Administration Oral
Dosage form Capsule 0 7 Gm

STRONTOLAC (Wyeth)
Trade name for Strontium Lactate

STROPHANTHIN
Available in hypodermic tablets of 0 3 and 0 6 mg for intravenous injection

STRYCHNINE as such and salts
Administration Oral, subcutaneous
Dosage forms Various forms

SURFACAINE (Lilly)
Trade name for Cyclomethycaine

SURGICAL PITUITRIN (Parke Davis)
Trade name for Posterior Lobe Pituitary Extract

SURGI CEN (Central)
Trade name for Hexachlorophene

SURITAL SODIUM (Parke Davis)
Trade name for Thiamylal Sodium

SUS PHRINE (Brewer)
Trade name for Epinephrine HCl

SUVREN (Ayerst)
Trade name for Captodiamine HCl

SUXINYL (Fougera)
Trade name for Succinylcholine Cl

SYCOTROL (Reed & Carnrick)
Trade name for Piperilate HCl

SYLNASOL (Searle)
Trade name for Sodium Psylliate

SYMPATOL (Winthrop)
Trade name for Synephrine Tartrate

SYNANDRETS (Pfizer)
Trade name for Methyltestosterone

SYNANDROL (Pfizer)
Trade name for Testosterone Propionate

SYNANDROL-F (Pfizer)
Trade name for Testosterone

SYNANDROTABS (Pfizer)
Trade name for Methyltestosterone

SYNATAN (Irwin Neisler)
Trade name for Tanphetamin Protocollo d

SYNCELOSE (Blue Line)
Trade name for Methylcellulose

SYNCURINE (Burroughs Wellcome)
Trade name for Decamethonium Br

SYNDROX (McNeil)
Trade name for Methamphetamine HCl

SYNEPHRINE TARTRATE
Trade name Sympatol (Winthrop)
Administration Oral subcutaneous
Dosage forms Tablet 0 1 Gm ampule 60 mg per ml

SYNERONE (Pitman Moore)
Trade name for Testosterone Propionate

SYNGESTERONE (Pfizer)
Trade name for Progesterone

SYNGESTROTABS (Pfizer)
Trade name for Ethisterone

SYNKAMIN (Parke Davis)
Trade name for Amino Methyl Naphthol HCl

SYNKAYVITE (Roche)
Trade name for Menadiol Sodium PO

SYNOPHYLATE (Central)
Trade name for Theophylline Sodium Glycinate

SYNTETRIN (Bristol)
Trade name for Tetracycline N (Pyrrolidinomethyl)

SYNTHROID SODIUM (Travenol)
Trade name for Sodium Levothyroxine

SYNTROPAN (Roche)
Trade name for Amprotropine PO

SYROSINGOPINE
Trade name Singoserp (Ciba)
Administration Oral
Dosage form Tablet 1 mg

SYTOBEX (Parke Davis)
Trade name for Cyanocobalamin

TACARYL (Mead Johnson)
Trade name for Methdilazine

TACE (Merrell)
Trade name for Chlorotrianisene

TAGATHEN (Lederle)
Trade name for Chlorothen Citrate

TAKA DIASTASE (Parke Davis)
Trade name for Diastase

TALBUTAL
Trade name Lotusate (Winthrop)
Administration Oral
Dosage form Tablets 30 50 and 120 mg

TALC
Synonym Talcum
Dosage form As such

TALCUM
Synonym for Talc

SULFAMETHAZINE
Administration Oral
Dosage form Tablet 0 5 Gm

SULFAMETHAZINE SULFADIAZINE SULFAMERAZINE MIXTURE
Synonym for Meth Dia Mer Sulfonamides

SULFAMETHIZOLE
Trade names Thiosulfil (Ayerst) Urosulfin (Nepera)
Administration Oral
Dosage forms Tablet 0 25 Gm suspens on 50 mg per ml

SULFAMETHOXYPYRIDAZINE
Trade name Kynex (Lederle) Midicel (Parke Davis)
Administration Oral
Dosage form Tablet 0 5 Gm

SULFAMETHOXYPYRIDAZINE ACETYL
Trade name Kynex Acetyl (Lederle)
Administration Oral
Dosage form Suspension 25 mg per ml

SULFAMYLON HCl (Winthrop)
Trade name for Mafen de HCl

SULFANILAMIDE
Administration Oral top cal
Dosage forms Tablet 0 5 Gm powder

SULFAPYRIDINE
Administration Oral
Dosage form Tablet 0 5 Gm

SULFASUXIDINE (Merck)
Trade name for Succinylsulfath azole

SULFATHALIDINE (Merck)
Trade name for Phthalylsulfathiazole

SULFATHIAZOLE
Administration Oral topical
Dosage forms Tablets 0 5 Gm and a va riety of forms

SULFATHIAZOLE-SULFADIAZINE SULFAMERAZINE MIXTURE
Synonym for Thia Dia Mer-Sulfonam des

SULFA TRI AZINE (Thompson)
Trade name for Meth D a Mer Sulfonamides

ULFERROUS (Chicago)
rade name for Ferrous SO

ULFINPYRAZONE
ade name Anturan (Geigy)
ministration Oral
age form Tablet 100 mg

SULFISOMIDINE
Trade name Elkosin (Ciba)
Administration Oral
Dosage forms Tablet 0 5 Gm suspe approximately 60 mg per ml

SULFISOXAZOLF
Trade name Gantrisin (Roche)
Administration Oral
Dosage forms Tablet 0 5 Gm solution mg per ml

SULFISOXAZOLE DIETHANOLAMINE
Trade name Gantrisin Diethanolamine (Roche)
Administration Topical
Dosage form Solution 4%

SULFOBROMOPHTHALEIN SODIUM
Trade name Bromsulphalein (Hynson)
Administration Intravenous
Dosage form Ampule 50 mg per ml

SULFONAMIDES DUPLEX (Lilly)
Trade name for D a Mer Sulfonamides

SULFONSOL (National)
Trade name for Meth Dia Mer Sulfonamides

SULFOSE (Wyeth)
Trade name for Meth Dia Mer Sulfonam des

SULFOXONE SODIUM
Trade name Diasone Sodium (Abbott)
Administration Oral
Dosage form Tablet 0 33 Gm

SUL-SPANSION (Smith Kline & French)
Trade name for Sulfaethidole

SUMYCIN (Squibb)
Trade name for Tetracycl ne PO Complex

SUPERFATTED SOAPS
Almay Superfatted Soap (Almay) Bas s Soap (Duke) Dove Soap (Lever) O latum (Steifel)

SUPERINONE
Trade name Alevaire (Winthrop)
Administration Inhalation
Dosage form Nebula 0 125%

SUPRANEPHRIN (Rorer)
Trade name for Epinephr ne HCl

SUPRARENIN (Winthrop)
Trade name for Ep nephrine Bitartrate

SUR BEX (Abbott)
Trade name for Vitamin B C

TESTOSTERONE
Trade names Androlin (Lincoln), Andronaq (Central), Andrusol (C D Smith), Aqua Testerone (Endocrine), Diphasol Testosterone (Kremers Urban), Malestrone (Kirk), *Mertestate (Breon)*, *Neo-Hombreol* (F) (Organon), Oreton F (Schering), Synandrol F (Pfizer), Testandrone (Carnrick), Testobase (Merck), Testosteroid (Sherman), Testrone (Miller), Testryl (Squibb)
Administration Buccal sublingual, intramuscular
Dosage forms Tablets, 3, 5, and 6 mg, vials 25 and 50 mg per ml

TESTOSTERONE CYCLOPENTYLPROPIONATE
Trade name Depo Testosterone (Upjohn)
Administration Intramuscular
Dosage form Vials, 50, 100 mg per ml

TESTOSTERONE ENANTHATE
Trade name Delatestryl (Squibb)
Administration Intramuscular
Dosage form Ampule, 200 mg per ml

TESTOSTERONE PHENYLACETATE
Trade name Perandren Phenylacetate (Ciba)
Administration Intramuscular
Dosage form Vial, 50 mg per ml

TESTOSTERONE PROPIONATE
Trade names Androlin in Oil (Lincoln), Andronate (Central), Andrusol P (C D Smith ... Neo-Hom breol ... andre ... rone
Administration Intramuscular
Dosage form Vials, 10 25 50, 100 mg per ml

TESTRONE (Miller)
Trade name for Testosterone

TESTRYL (Squibb)
Trade name for Testosterone

TETRABON (Pfizer)
Trade name for Tetracycline HCl

TETRACAINE HCl
Synonym Amethocaine HCl
Trade name Pontocaine HCl (Winthrop)
Administration Topical parenteral
Dosage forms A large variety of forms

TETRACHLOROETHYLENE
Administration Oral
Dosage form Capsules, 0 2, 1 0, 2 5 ml

TETRACYCLINE
Trade names Achromycin (Lederle), Panmycin (Upjohn), Polycyline (Bristol), Tetracyn (Roerig)
Administration Oral
Dosage forms Capsules, tablets, 50, 100, 250 mg

TETRACYCLINE HCl
Trade names Achromycin HCl (Lederle), Panmycin HCl (Upjohn), Polycycline HCl (Bristol), Steclin (Squibb), Tetrabon (Pfizer), Tetracyn HCl (Roerig)
Administration Oral, parenteral, topical
Dosage forms A variety of forms

TETRACYCLINE N-(PYRROLIDINOMETHYL)
Trade name Syntetrin (Bristol)
Administration Intravenous intramuscular
Dosage form Vials 150, 350 mg

TETRACYCLINE PO_4 BUFFERED
Trade names Achromycin V (Lederle), Tetracyn V (Pfizer)
Administration Oral
Dosage form Capsules, 50, 100, 250 mg

TETRACYCLINE PO_4 COMPLEX
Trade names Panmycin PO_4 (Upjohn), Sumycin (Squibb), Tetrex (Bristol)
Administration Oral
Dosage form Capsules, 50 100, 250 mg

TETRACYN (Roerig)
Trade name for Tetracycline

TETRACYN HCl (Roerig)
Trade name for Tetracycline HCl

TETRACYN V (Pfizer)
Trade name for Tetracycline PO_4 Buffered

TETRAETHYLAMMONIUM Cl
Synonym TEA
Trade name Etamon (Parke Davis)
Administration Intravenous, intramuscular
Dosage form Vial 100 mg per ml

TETRAHYDROZOLINE HCl
Trade name Tyzine (Pfizer), Visine (Pfizer)
Administration Intranasal topical
Dosage form Solution 0 1%, 0 05%

TETRAIODOPHENOLPHTHALEIN SODIUM
Synonym for Iodophthalein Sodium

TETRANTOIN
Trade name Spirodon (Cutter)
Not available on the commercial drug market

TALSUTIN (Squibb)
Trade name for Phthalylsulfacetamide

TANNIC ACID
Synonym Gallotannic Acid
Administration Topical oral by lavage
Dosage form Powder, glycerite and ointment

TANPHETAMINE PROTOCOLLOID
Trade name Synatan (Irwin Neisler)
Administration Oral
Dosage form Tablet 17 5 mg (equivalent to 5 25 mg Amphetamine)

TAO (Roerig)
Trade name for Triacetyloleandomycin

TAPAZOLE (Lilly)
Trade name for Methimazole

TARBONIS (Reed & Carnrick)
Proprietary Tar extract 5%

TARCORTIN (Reed & Carnrick)
Trade name for preparation containing Hydrocortisone 0 5% in Tarbonis

TEA
Synonym for Tetraethylammonium Cl

TEDRAL (Warner Chilcott)
Each tablet contains Theophylline 0 13 Gm Ephedrine HCl 24 mg Phenobarbital 8 mg

TELDRIN (Smith Kline & French)
Trade name for Chlorpheniramine Maleate

TELEPAQUE (Winthrop)
Trade name for Iopanoic Acid

TELMID (Lilly)
Trade name for Dithiazanine I

TEM
Synonym for Triethylene Melamine

TEMARIL (Smith Kline & French)
Trade name for Trimeprazine Tartrate

TEMPOSIL (Lederle)
Trade name for Citrated Calcium Carbimide

TEMPRA (Mead Johnson)
Trade name for Acetaminophen

TENSILON Cl (Roche)
Trade name for Edrophonium Cl

TENTONE (Lederle)
Trade name for Methoxypromazine Maleate

TENUATE (Merrell)
Trade name for Diethylpropion

TEPANIL (National)
Trade name for Diethylpropion

TERFONYL (Squibb)
Trade name for Meth Dia Mer Sulfonamides

TERGEMIST (Abbott)
Trade name for Tergitol 08 and Potassium I

TERGITOL 08 (Abbott)
Detergent

TERIDAX (Schering)
Trade name for Iophenoxic Acid

TEROPTERIN (Lederle)
Trade name for Pteroyl Triglutamate Sodium

TERPIN HYDRATE
Administration Oral
Dosage form Elixir

TERRABON (Pfizer)
Trade name for Oxytetracycline

TERRA CORTRIL (Pfizer)
Proprietary ointment containing Hydrocortisone 1% and Terramycin 3%

TERRAMYCIN (Pfizer)
Trade name for Oxytetracycline

TERRAMYCIN HCl (Pfizer)
Trade name for Oxytetracycline HCl

TERSASEPTIC (Doak)
Hexachlorophene soap

TERTIASUL (Rorer)
Trade name for Acet Dia Mer Sulfonamides

TESSALON (Ciba)
Trade name for Benzonatate

TESTANDRONE (Carnrick)
Trade name for Testosterone

TESTOBASE (Merck)
Trade name for Testosterone

TESTODET (Merck)
Trade name for Testosterone Propionate

TESTOSTEROID (Sherman)
Trade name for Testosterone

THEPHORIN (Roche)
Trade name for Phenindamine Tartrate

THERUHISTIN (Ayerst)
Trade name for Isothipendyl HCl

THESODATE (Brewer)
Trade name for Theobromine and Sodium Acetate

THEVETIN
Not available on the commercial drug market

THIA-DIA MER SULFONAMIDES
Synonym Sulfathiazole Sulfadiazine Sulfamerazine Mixture
Trade name Thi Di Mer (Pitman Moore)
Administration Oral
Dosage form Tablet, 0 5 Gm

THIAMINE HCl
Synonym Vitamin B_1
Trade names Betalin S (Lilly), Betaxin (Winthrop), Thiamintol (Rorer), Thibex (Brewer), and many others
Administration Oral, parenteral
Dosage forms Tablets of many sizes ampules, 1 ml containing 10, 50, or 100 mg

THIAMINTOL (Rorer)
Trade name for Vitamin B_1

THIAMYLAL SODIUM
Trade name Surital Sodium (Parke, Davis)
Administration Intravenous rectal
Dosage forms Vials, 0 2, 0 3, 0 5, 1 0 5 0, 10 Gm nonsterile for rectal, 1 5, 3 0 Gm

THIANTOIN (Lilly)
Trade name for Phethenylate Sodium

THIAZOLSULFONE
Trade name Promizole (Parke, Davis)
Administration Oral
Dosage form Tablet, 0 5 Gm

THIBEX (Brewer)
Trade name for Vitamin B

THI DI MER (Pitman Moore)
Trade name for Thia Dia Mer Sulfonamides

THIMECIL (Physicians)
Trade name for Methylthiouracil

THIMEROSAL
Trade name Merthiolate (Lilly)
Administration Topical
Dosage forms A variety of forms

THIO BISMOL (Parke, Davis)
Trade name for Sodium Bismuth Thioglycollate

THIOCARBARSONE (Lilly)
Trade name for Carbamidophenyl di (carboxymethylthio) Arsenite

6-THIOGUANINE
Not available on the commercial drug market

THIOMERIN (Wyeth)
Trade name for Mercaptomerin

THIOPENTAL SODIUM
Trade name Pentothal Sodium (Abbott)
Administration Intravenous rectal
Dosage forms Ampules, 0 5 1 0 Gm, non sterile for rectal, 1 5, 3 0 Gm

THIOPERAZINE
Synonym Vontil
Not on commercial drug market

THIOPROPAZATE HCl
Trade name Dartal HCl (Searle)
Administration Oral
Dosage form Tablets, 5 and 10 mg

THIORIDAZINE HCl
Trade name Mellaril (Sandoz)
Administration Oral
Dosage form Tablets 10, 25, 100 mg

THIOSEMICARBAZONE
Synonym for Amithiozone

THIOSULFIL (Ayerst)
Trade name for Sulfamethizole

THIO-TEPA
Synonym for Triethylene Thiophosphoramide

THIXOKON (Mallinckrodt)
Trade name for Sodium Acetrizoate

THONZYLAMINE HCl
Trade names Anahist (Anahist), Neohetramine (Nepara), Resistab (Bristol Meyers)
Administration Oral topical
Dosage forms Tablets 25, 50, 100 mg, syrup, 6 25 mg per ml, cream, 2%

THORAZINE (Smith, Kline & French)
Trade name for Chlorpromazine HCl

THORIUM DIOXIDE
Trade names Thorotrast (Testagar), Umbrathor (Heyden)
Administration Intravenous, intra arterial, oral, rectal, urethral
Dosage form Ampule 25%

THORIUM X (Fleischman, Burd)
Trade name for Radioactive Thorium

THOROTRAST (Testagar)
Trade name for Thorium Dioxide

TETREX (Bristol)
Trade name for Tetracycl ne PO Complex

THALAMYD (Schering)
Trade name for Phthalylsulfacetamide

THALISUL (Massengill)
Trade name for Phthalylsulfacetamide

THEELIN (Parke Davis)
Trade name for Estrone

THEELOL (Parke Davis)
Trade name for Estriol

THELESTRIN (Carnrick)
Trade name for Estrone

THENFADIL HCl (Winthrop)
Trade name for Thenyldiamine HCl

THENYLDIAMINE HCl
Trade name Thenfad l (Winthrop)
Administration Oral
Dosage form Tablet 15 30 mg

THENYLENE (Abbott)
Trade name for Methapyrilene HCl

THENYLPYRAMINE
Synonym for Methapyrilene

THEOBROMINE AND SODIUM ACETATE
Trade name Thesodate (Brewer)
Administration Oral
Dosage form Tablets 0 25 and 0 5 Gm

THEOBROMINE AND SODIUM SALICYLATE
Trade name Diuretin (B lhuber Knoll)
Administration Oral
Dosage form Tablet 0 5 Gm

THEOBROMINE CALCIUM SALICYLATE
Trade names Phyllicin (Bilhuber Knoll) Theocalcin (Bilhuber Knoll)
Administration Oral
Dosage form Tablets 0 3 and 0 5 Gm

THEOCALCIN (Bilhuber Knoll)
Trade name for Theobromine Calcium Salicylate

THEOCIN (Winthrop)
Trade name for Theophylline

THEOCIN SOLUBLE (Winthrop)
Trade name for Theophylline and Sod um Acetate

THEOGLYCINATE (Brayten)
Trade name for Theophyll ne Sodium Glycinate

THEOMERSYL (Central)
Trade name for Mersalyl with Theophyll ne Sodium Glycinate

THEOPHYLLINE
Trade name Theocin (Winthrop)
Administration Oral
Dosage form Tablets 0 1 and 0 2 Gm

THEOPHYLLINE AND SODIUM ACETATE
Trade name Theocin Soluble (Winthrop)
Administration Oral
Dosage form Tablet (coated), 0 2 Gm

THEOPHYLLINE CALCIUM SALICYLATE
Trade name Phyll c n (B lhuber Knoll)
Administration Oral
Dosage form Tablet 0 6 Gm

THEOPHYLLINE ETHYLENEDIAMINE
Synonym for Aminophylline

THEOPHYLLINE ISOPROPANOLAMINE
Trade name Theopropanol (National Drug)
Administration Oral intramuscular intravenous
Dosage forms Tablets 0 1 and 0 2 Gm vials for intramuscular injection, 2 ml containing 0 5 Gm for intravenous injection 10 ml contain ng 0 25 Gm

THEOPHYLLINE METHYLGLUCAMINE
Trade name Glucophylline (Abbott)
Administration Oral rectal parenteral
Dosage forms Tablets enteric-coated 0 15 and 0 3 Gm suppository 0 5 Gm intramuscular injection 0 73 Gm in 2 ml intravenous injection 0 37 Gm in 10 ml

THEOPHYLLINE MONOETHANOLAMINE
Trade name Clysmathane (Fleet) Monotheamin (Lilly)
Administration Oral, intravenous rectal
Dosage forms Tablet 0 2 Gm ampule, 25 mg per ml squeeze bottle, 625 mg

THEOPHYLLINE SODIUM GLYCINATE
Trade names *Dorsaphyll n (Dorsey) Pemo-* [illegible]

Gm in 20 ml

THEOPROPANOL (Roche)
Trade name for Theophylline Isopropanolamine

TOLFRON (Mallinckrodt)
Trade name for Ferrous Fumarate

TOLHART (Hart)
Trade name for Mephenesin

TOLONIUM Cl
Synonym Toluidine Blue
Trade name Blutene Cl (Abbott)
Administration Oral
Dosage form Tablet, 100 mg

TOLOSATE (Brewer)
Trade name for Mephenesin

TOLPAL (Philadelphia)
Trade name for Tolazoline HCl

TOLSERAM (Squibb)
Trade name for Mephenesin Carbamate

TOLSEROL (Squibb)
Trade name for Mephenesin

TOLUIDINE BLUE
Synonym for Tolonium Cl

TOLULOX (Miller)
Trade name for Mephenesin

p-TOLYLMETHYL-CARBINOL MONO-d-CAMPHORATE DIETHANOLAMINE
Trade name Gallogen (Massengill)
Administration Oral
Dosage form Tablet, 75 mg

TOLYSIN (Lederle)
Trade name for Neocinchophen

TOPITRACIN (C.S C.)
Trade name for Bacitracin

TOPOCIDE (Lilly)
Trade name for emulsion containing Benzyl Benzoate, DDT, and Ethyl Aminobenzoate

TORANTIL (Winthrop)
Trade name for Histaminase

TORYN (Smith, Kline & French)
Trade name for Caramiphen Ethanedisulfonate

TOTAQUINE
Administration Oral
Dosage forms A variety of forms

TRAL (Abbott)
Trade name for Hexocyclium Methylsulfate

TRANCOPAL (Winthrop)
Trade name for Chlormezanone

TRASENTINE (Ciba)
Trade name for Adiphenine HCl

TRAVAD (Travenol)
Trade name for Sodium PO_4 solution

TRAVERT (Baxter)
Trade name for Invert Sugar

TRETHYLENE (Davis, Rose)
Trade name for Trichloroethylene

TRIACETIN
Synonym Glyceryl Triacetate
Trade names Enzactin (Ayerst), Fungacetin (Harvey)
Dosage forms Ointment, 0 5 to 10%

TRIACETYLOLEANDOMYCIN
Trade names Cyclamycin (Wyeth), Tao (Roerig)
Administration Oral
Dosage forms Capsules, 125 and 250 mg, suspension, 25 mg per ml

TRIACETYL PYROGALLOL
Synonym for Acetpyrogall

TRIAMCINOLONE
Trade names Aristocort (Lederle), Kenacort (Squibb)
Administration Oral
Dosage form Tablets, 2 and 4 mg

TRIAMCINOLONE ACETONIDE
Trade name Kenalog (Squibb)
Administration Topical
Dosage forms Cream, lotion, ointment, 0 1%

TRIBROMOETHANOL
Trade name Avertin (Winthrop)
Administration Rectal
Dosage form Solution, 2 5% with Amylene Hydrate

TRIBURON (Roche)
Trade name for Triclobisonium Cl

TRICHLOROACETIC ACID
Administration Topical
Dosage forms Crystals or highly concentrated solutions

TRICHLOROETHYLENE
Trade names Chlorylen (Schering), Trethylene (Davis, Rose), Trilene (Ayerst)
Administration Inhalation
Dosage form Container, as such

TRICLOBISONIUM Cl
Trade name Triburon (Roche)
Administration Topical
Dosage forms Ointment, 0 1%, cream, 0 1%

THOXIDIL (Normand)
Trade name for Mephenes n

THROMBIN
Administration Topical oral
Dosage form Vials 1 000 5 000 and 10 000 units to be diluted to 1 000 units per ml

THROMBOL (Merck)
Trade name for Thromboplastin

THROMBOPLASTIN
Synonym Brain Extract Solut on
Trade name Thrombol (Merck)
Administration Topical oral subcutaneous intravenous
Dosage form Vial 20 ml

THROMBOPLASTIN SUSPENSION
Trade name Thrombol (Merck)
Administration Topical subcutaneous
Dosage form Vial 20 ml

THYLOGEN (Rorer)
Trade name for Pyrilamine Maleate

THYLOKAY (Squibb)
Trade name for Menad ol Sodium PO

THYMOL
Administration Topical
Dosage forms Var ous forms

THYMOL I
Trade name Aristol (Merck)
Administration Top cal
Dosage form As such

THYRACTIN (Winthrop)
Trade name for Prothyrin

THYRAR (Armour)
Trade name for Thyro d

THYROGLOBULIN
Trade names Endothyrin (Harrower) Proloid (Warner Ch lcott
Administration Oral
Dosage forms Tablets 16 32 65 100 3?5 mg powder

THYROID
Trade name Thyrar (Armour)
Administration Oral
Dosage forms Tablets 15 30 60 120 mg

THYROPROTEIN
Administration Subcutaneous
Dosage form Ampule 1 3 mg per ml

THYROTROPIN
Trade name Thytropar (Armour)
Administration Intramuscular subcutaneous
Dosage Vial 10 U S P units

THYROXIN
Administration Intravenous
Dosage form Ampule 100 mg

THYTROPAR (Armour)
Trade name for Thyrotrop n

TIBIONE (Schenley)
Trade name for Amithiozone

TIGAN (Roche)
Trade name for Tr methobenzamide HCl

TISIN (Arlington)
Trade name for Isoniazid

TITANIUM DIOXIDE
Administration Top cal
Dosage forms Up to 25% in powders creams and emulsions

TITRALAC (Schenley)
Trade name for Aminoacetic Acid and Calcium Carbonate

TOCLASE (Pfizer)
Trade name for Carbetapentane Citrate

TOCOPHEREX (Squibb)
Trade name for Tocopherols Mixed

TOCOPHEROLS MIXED
Synonym Vitamin E
Trade names Cotopherol (Endo) Ecofrol (Breon), Ephynal (Roche) Eprolin (Lilly) Epsilan (Warren Teed) Esorb (Wyeth) E Toplex (U S Vitamin), Tocopherex (Squibb) Tocophrin (Barry) Tofaxin (Winthrop) and many others
Dosage form Many forms

TOCOPHRIN (Barry)
Trade name for Tocopherols Mixed

TOFAXIN (Winthrop)
Trade name for Tocopherols Mixed

TOFRANIL (Geigy)
Trade name for Imipramine HCl

TOLANATE (C.S C.)
Trade name for Inositol Hexanitrate

TOLAZOLINE HCl
Trade names Priscoline (C ba) Tolpal (Philadelphia)
Administration Oral subcutaneous intramuscular intravenous
Dosage forms Tablet 26 mg el xir 6 mg per ml vial 25 mg per ml

TOLBUTAMIDE
Trade name Orinase (Upjohn)
Administration Oral
Dosage form Tablet 0 5 Gm

TRIPROLIDINE HCl
Trade name Actidil (Burroughs Wellcome)
Administration Oral
Dosage forms Tablet, 2 5 mg, syrup, 0 25 mg per ml

TRISEM (Massengill)
Trade name for Meth Dia Mer Sulfonamides

TRI-SIL (Warren Teed)
Trade name for Magnesium Trisilicate

TRISOGEL (Lilly)
Trade name for Magnesium Trisilicate and *Aluminum Hydroxide*

TRI SULFAMETH (Arlington)
Trade name for Meth Dia Mer Sulfonamides

TRISULFAZINE (Central)
Trade name for Meth Dia Mer Sulfonamides

TRITHEON (Ortho)
Trade name for Aminitrozole

TRIZH (Central)
Trade name for Acet Dia Mer Sulfonamides

TROMEXAN ETHYL ACETATE (Geigy)
Trade name for Ethyl Biscoumacetate

TRONOTHANE (Abbott)
Trade name for Pramoxine HCl

TROSINONE (Abbott)
Trade name for Ethisterone

TRUOZINE (Abbott)
Trade name for Meth Dia Mer Sulfonamides

TRYPSIN
Trade names Parenzyme (National), Tryptar (Armour)
Administration Inhalation, parenteral
Dosage forms Aerosol, 10 mg per ml vials 5 mg per ml in oil, 5 mg per ml

TRYPTAR (Armour)
Trade name for Trypsin

TSPA
Synonym for Triethylene Thiophosphoramide

TUBADIL (Endo)
Trade name for Tubocurarine Cl

TUBARINE (Burroughs Wellcome)
Trade name for Tubocurarine Cl

TUBARINE Cl (Burroughs Wellcome)
Trade name for Tubocurarine Cl

TUBOCURARINE Cl
Trade names Tubadil (*Endo*), *Tubarine (Burroughs Wellcome)*
Administration Intramuscular, intravenous
Dosage form Solutions, 3 15, 30 mg per ml

d TUBOCURARINE Cl
Synonym for Tubocurarine Cl

TURPENTINE OIL
Administration Oral
Dosage form As such

TUSSIONEX (Strasenburgh)
Mixture of Phenyltoloxamine and Dihydro codeinone

TWEEN 20
Synonym for Polysorbate 20

TWEEN 80
Synonym for Polysorbate 80

TYLENOL (McNeil)
Trade name for Acetaminophen

TYROTHRICIN
Trade name Soluthricin (Merck)
Administration Topical
Dosage form Solutions, 0 5 2 5 mg per ml

TYVID (Merrell)
Trade name for Isoniazid

TYZINE (Pfizer)
Trade name for *Tetrahydrozoline HCl*

ULTANDREN (Ciba)
Trade name for Fluoxymesterone

ULTRA LENTE ILETIN (Lilly)
Trade name for Ultralente Insulin

ULTRALENTE INSULIN
Trade name Ultra Lente Iletin *(Lilly)*
Administration Subcutaneous
Dosage forms Vials, 40 U per ml, 80 U per ml

ULTRAN (Lilly)
Trade name for Phenaglycodol

UMBRATHOR (Heyden)
Trade name for Thorium D oxide

UNDECYLENIC ACID
Trade name Desenex (Wallace & Tiernan)
Administration Oral
Dosage form Solution, 10%

UNDESOL (Veltex)
Trade name for Zincundecate

UNIDIGIN (Merrell)
Trade name for Digitoxin

TRICOFURON (Eaton)
Trade name for Furazolidone

TRICOLOID SO (Burroughs Wellcome)
Trade name for Tricyclamol SO_4

TRICOMBISUL (Schering)
Trade name for Acet Dia Mer Sulfonamides

TRI CREAMALATE (Winthrop)
Trade name for Magnesium Trisilicate and Aluminum Hydroxide

TRICYCLAMOL SO
Trade names Elorine SO (Lilly) Tricoloid (Burroughs Wellcome)
Administration Oral
Dosage form Capsule 25 mg

TRIDIHEXETHIDE
Trade name Pathilon (Lederle)
Administration Oral
Dosage form Tablet 25 mg

TRIDIONE (Abbott)
Trade name for Trimethadione

TRIETHANOLAMINE
Emulsifier

TRIETHANOLAMINE SALICYLATE
Trade name Myoflex Creme (Warren Teed)
Dosage form Cream 10%

TRIETHYLENE MELAMINE
Synonym TEM
Administration Oral
Dosage form Tablets 1 and 5 mg

TRIETHYLENE THIOPHOSPHORAMIDE
Synonyms TSPA Thio-TEPA
Not available on commercial drug market

TRIFLUOPERAZINE
Trade name Stelazine (Smith Kline & French)
Administration Oral
Dosage form Tablet 1 mg

TRIFLUPROMAZINE HCl
Trade name Vesprin (Squibb)
Administration Oral
Dosage form Tablets 10 25 and 50 mg

RIFONAMIDE (VanPelt & Brown)
ade name for Meth Dia Mer Sulfonamides

IHEXYPHENIDYL HCl
ade names Artane HCl (Lederle) Pipanol (Winthrop)
ninistration Oral
age forms Tablet 2 5 mg elixir 0 5 g per ml

L TRIIODOTHYRONINE
Synonym for Liothyronine

TRILAFON (Schering)
Trade name for Perphenazine

TRILENE (Ayerst)
Trade name for Trichloroethylene

TRIMEPRAZINE TARTRATE
Trade name Temaril (Smith Kline & French)
Administration Oral
Dosage form Tablet 2 5 mg

TRIMETHADIONE
Trade name Tridione (Abbott)
Administration Oral
Dosage forms Capsule 0 3 Gm tablet 150 mg solution about 30 mg per ml

TRIMETHAPHAN CAMPHORSULFONATE
Trade name Arfonad (Roche)
Administration Intravenous drip
Dosage form Ampule 50 mg per ml

TRIMETHIDINIUM METHOSULFATE
Trade name Ostensin (Wyeth)
Administration Oral
Dosage form Tablets 20 40 mg

TRIMETHOBENZAMIDE HCl
Trade name Tigan (Roche)
Administration Oral rectal intramuscular
Dosage forms Capsule 100 mg pediatric suppositories 200 mg ampule 100 mg per ml

TRIMETHYLENE
Synonym for Cyclopropane

TRIMETON (Schering)
Trade name for Pheniramine Maleate

TRINESIUM (Abbott)
Trade name for Magnesium Trisilicate

TRIONAMIDE (Flint Eaton)
Trade name for Meth Dia Mer Sulfonamides

TRIONINE (Roche)
Trade name for Liothyronine

TRIPAZINE (Eaton)
Trade name for Meth Dia Mer Sulfonamides

TRIPELENNAMINE HCl
Trade name Pyribenzamine (Ciba)
Administration Oral topical
Dosage forms Tablets 25 50 mg fluid equivalent of 5 mg per ml ointment 20 mg per Gm cream, 20 mg per ml

VERSENATE, CALCIUM DISODIUM (*Riker*)
Trade name for Edathamil Calcium Disodium

VESPRIN (Squibb)
Trade name for Triflupromazine HCl

VIADRIL (Pfizer)
Trade name for Hydroxydione

VIBAZINE HCl (Pfizer)
Trade name for Buclizine HCl

VICIN (Brewer)
Trade name for Ascorbic Acid

VINACTANE SO₄ (Ciba)
Trade name for Viomycin SO₄

VINBARBITAL SODIUM
Trade name Delvinal (Merck)
Administration Oral
Dosage form Capsules, 30, 100, and 200 mg

VINETHENE (Merck)
Trade name for Vinyl Ether

VINOBEL (Merrell)
Trade name for Belladonna Extract

VINYL ETHER
Synonym Divinyl Oxide
Trade name Vinethene (Merck)
Administration Inhalation
Dosage form Bottles, as such

VIOCIN (Pfizer)
Trade name for Viomycin SO₄

VIOFORM (Ciba)
Trade name for Iodochlorhydroxyquin

VIOKASE (VioBin)
Trade name for Pancreas

VIOMYCIN SO₄
Trade names Vinactane SO₄ (Ciba), Viocin (Pfizer)
Administration Intramuscular
Dosage form Ampule 1 Gm

VIOSTEROL
Synonym for Calciferol

VISAMMIN
Synonym Khellin
Trade names Ammivin (National Drug), Khelisem (Massengill)
Administration Oral
Dosage form Tablets 10, 20, and 25 mg

VISINE (*Pfizer*)
Trade name for Tetrahydrozoline HCl

VISTARIL (Pfizer)
Trade name for Hydroxyzine Pamoate

VITADEX B (Cutter)
Trade name for Vitamin B Complex

VITAMIN A
Synonym for Oleovitamin A

VITAMIN A, WATER MISCIBLE
Trade names Acon (Endo), Aquasol (U S Vitamin), and many others
Administration Oral intramuscular
Dosage form Solution, 25,000 U per ml

VITAMIN B
Synonym for Thiamine HCl

VITAMIN B_2
Synonym for Riboflavin

VITAMIN B_6
Synonym for Pyridoxine HCl

VITAMIN B_{12}
Synonym for Cyanocobalamin

VITAMIN B COMPLEX
Nonproprietary preparations Brewer's Yeast, Yeast Concentrate
Trade names Beta Concemin (Merrell) Betalin (Lilly), Betaplexin (Winthrop), Desiver (U S Vitamin), Heptobee (Endo), Lederplex (Lederle), Solu Zyme (Upjohn), Sur Bex (Abbott), Vitadex B (Cutter), and many others
Administration Oral parenteral
Dosage forms A large variety of forms

VITAMIN C
Synonym for Ascorbic Acid

VITAMIN D_2
Synonym for Calciferol

VITAMIN E
Synonym for Tocopherols Mixed

VITAMIN G
Synonym for Riboflavin

VITAMIN K
Synonym for Menadione

VITAMIN K, SYNTHETIC
Synonym for Menadione

VITAMIN K_1
Synonym for Phytonadione

VITAMIN P
Synonym for Hesperidin Methyl Chalcone

UNITENSEN (Irwin Neisler)
Trade name for Cryptenamine

UNITENSEN TANNATE (Irwin Neisler)
Trade name for Cryptenamine Tannate

UREA
Synonym Carbamide
Administration Oral
Dosage form Solution various concentrations

URECHOLINE Cl (Merck)
Trade name for Bethanechol Cl

URETHAN
Synonym Ethyl Carbamate
Administration Oral
Dosage form Tablet 0 3 Gm

URGININ
Administration Oral
Dosage form Tablet 0 5 mg

URITONE (Parke Davis)
Trade name for Methenamine

UROENTERONE
Trade name Kutrol (Parke Davis)
Administration Oral
Dosage form Capsule 75 mg

UROKON SODIUM (Mallinckrodt)
Trade name for Sodium Acetrizoate

UROSULFIN (Nepera)
Trade name for Sulfamethizole

UROSULFON (C M C)
Trade name for Sulfacetamide

UROTROPIN (Warner Chilcott)
Trade name for Methenamine

VALETHAMATE Br
Trade name Murel (Ayerst)
Administration Oral intravenous intramuscular
Dosage forms Tablet 10 mg vial 10 mg per ml

VALLESTRIL (Searle)
Trade name for Methallenestril

VALMID (Lilly)
Trade name for Ethinamate

VANCOCIN (Lilly)
Trade name for Vancomycin

VANCOMYCIN
Trade name Vancocin (Lilly)
Administration Intravenous
Dosage form Ampule 500 mg

VANOGEL (VanPelt & Brown)
Trade name for Aluminum Hydroxide

VANQUIN (Parke Davis)
Trade name for Pyrvinium Cl

VANZOATE (VanPelt & Brown)
Trade name for Benzyl Benzoate

VAPONEFRIN
Trade name for Epinephrine HCl (2 25 solution in a nebulizer

VARIDASE (Lederle)
Trade name for Streptokinase Streptodornase

VASCULAT
Not available on the commercial drug market

VASODILAN (Mead Johnson)
Trade name for Isoxsuprine

VASODRINE (Premo)
Trade name for Epinephrine HCl

VASOPRESSIN
Trade name Pitressin (Parke Davis)
Administration Intramuscular subcutaneous
Dosage form Vial 20 Pressor units per ml

VASOPRESSIN TANNATE
Trade name Pitressin Tannate
Administration Intramuscular
Dosage form Ampule 5 units per ml in oil

VASOXYL (Burroughs Wellcome)
Trade name for Methoxamine HCl

V CILLIN (Lilly)
Trade name for Phenoxymethyl Penicillin

VENOM RUSSELL VIPER
Trade name Stypven (Burroughs Wellcome)
Administration Topical
Dosage form Vial as such for solution

VENTRICULIN (Parke Davis)
Trade name for Stomach Powdered

VERALBA (Pitman Moore)
Trade name for Protoveratrines A and B

VERILOID (Riker)
Trade name for Alkavervir

VERITOL
Not available on the commercial drug market

VERMIZINE (Chicago)
Trade name for Piperazine Gluconate

VERONAL
Synonym for Barbital

VITAMIN P FACTOR
Synonym Rutin
Administration Oral
Dosage form Tablets 20 50 100 250 mg

VITRAL (Flint, Eaton)
Trade name for Cyanocobalamin

VLEM DOME POWDER PACKETS (Dome)
Calcium polysulfide calcium thiosulfate sul fur powder

VONEDRINE (Merrell)
Trade name for Phenylpropylmethylamine HCl

VONTIL
Synonym for Thioperazine

WARCOUMIN (Harvey)
Trade name for Warfarin Sodium

WARFARIN SODIUM
Trade names Coumadin Sodium (Endo) Warcoumin (Harvey)
Administration Oral intravenous
Dosage forms Tablets 5, 10, 25 mg am pule 75 mg per ml

WHITE LOTION
Synonym Lotio Alba
Administration Topical
Dosage forms Suspension zinc oxide and sulfurated potash, 4%

WHITE PRECIPITATE
Synonym for Ammoniated Mercury

WILD CHERRY
Administration Oral
Dosage form Syrup

WYAMINE (Wyeth)
Trade name for Mephentermine SO_4

WYCILLIN (Wyeth)
Trade name for Procaine Penicillin G

WYDASE (Wyeth)
Trade name for Hyaluronidase

WYNESTRON (Wyeth)
Trade name for Estrone

XEROFORM (Merco)
Trade name for Bismuth Tribromophenate

XYLOCAINE HCl (Astra)
rade name for Lidocaine HCl

XYLOMETAZOLINE HCl
ade name Otrivin (Ciba)
ministration Topical
sage form Solution 0 1 and 0 05%

YATREN
Synonym for Chiniofon

YEAST CONCENTRATE
Synonym for Vitamin B Complex

YODOXIN
Trade name for Diiodohydroxyquin

ZACTANE (Wyeth)
Trade name for Ethoheptazine Citrate

ZACTIRIN (Wyeth)
Trade name for mixture of Aspirin a Ethoheptazine

ZANCHOL (Searle)
Trade name for Florantyrone

ZEPHIRAN Cl (Winthrop)
Trade name for Benzalkonium Cl

ZETAR EMULSION (Dermik)
Crude Coal Tar

ZETAR SHAMPOO (Dermik)
Tar shampoo

ZINC INSULIN CRYSTALLINE
Administration Subcutaneous
Dosage form Vials, 40 and 80 units per ml

ZINC OXIDE
Administration Topical
Dosage forms Various forms

ZINC PEROXIDE
Administration Topical
Dosage form Suspension 40%

ZINC SO_4
Administration Topical
Dosage form Solution 1 to 4%

ZINC STEARATE
Administration Topical
Dosage form Powder about 15%

ZINCHLORUNDESAL
Trade name Salundek (Wallace & Tiernan)
Administration Topical
Dosage form Ointment 20%

ZINCUNDECATE
Trade name Undesol (Veltex)
Administration Topical
Dosage form Ointment 50%

ZOXAZOLAMINE
Trade name Flexin (McNeil)
Administration Oral
Dosage form Tablet, 250 mg

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